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Patentanmeldung Nr. Patent application No. Demande de brevet n°

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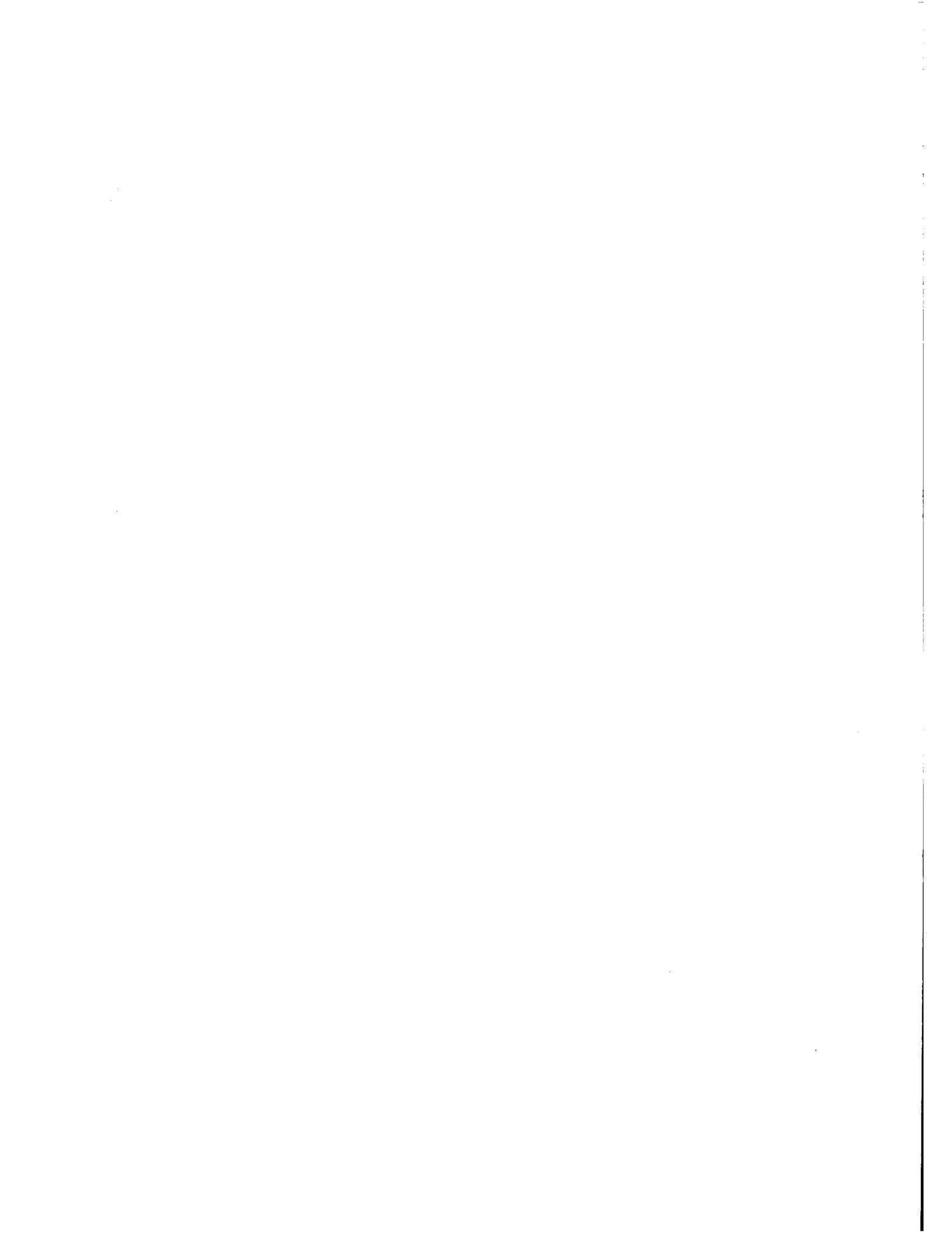
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Protein complexes associated with the processing of the APP-protein

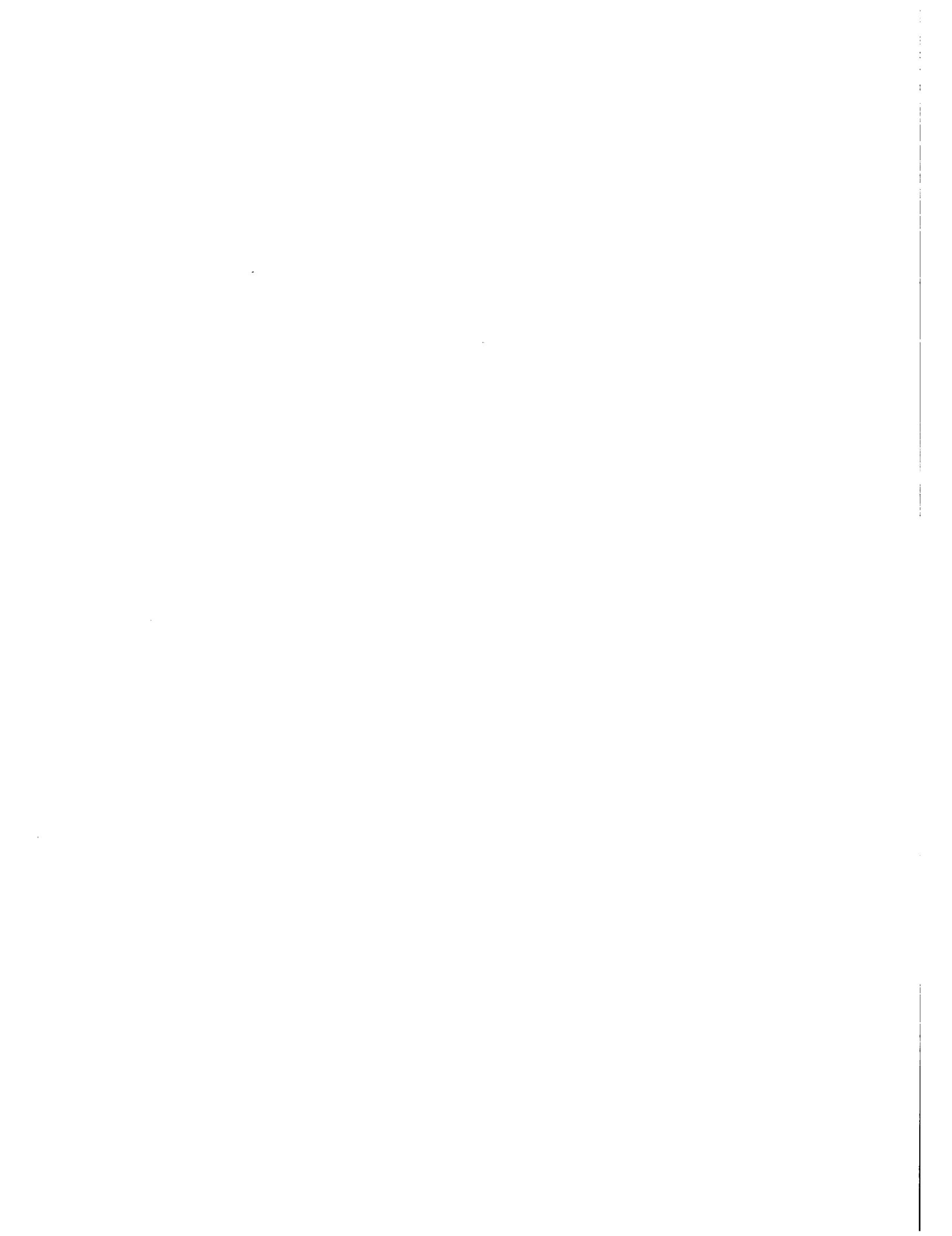
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## PROTEIN COMPLEXES ASSOCIATED WITH THE PROCESSING OF APP-PROTEIN

### 1. FIELD OF THE INVENTION

The present invention relates to protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

### 2. BACKGROUND OF THE INVENTION

Alzheimer's disease is a chronic condition that affects millions of individuals worldwide. After onset of the disease sufferers require a high degree of supervision and care. As the proportion of aged individuals in the population increases, the number of sufferers of Alzheimer's disease is expected to expand dramatically. Current top drugs (e.g. Aricept®/donepezil) attempt to achieve a temporary improvement of cognitive functions by inhibiting acetylcholinesterase, which results in increased levels of the neurotransmitter acetylcholine in the brain. These therapies are not suitable for later stages of the disease, they do not treat the underlying disease pathology, and they do not halt disease progression. The growing need for an effective therapy, coupled with the absence of effective treatments, presents a significant opportunity for drug target development and drug discovery.

The brains of sufferers of Alzheimer's disease show a characteristic pathology of prominent neuropathologic lesions, such as the initially intracellular neurofibrillary tangles (NFTs), and the extracellular amyloid-rich senile plaques. These lesions are associated with massive loss of populations of CNS neurons and their progression accompanies the clinical dementia associated with AD. The major component of amyloid plaques is the amyloid beta peptide. Amyloid beta is the proteolytic product of a precursor protein, beta amyloid precursor protein (beta-APP or APP). APP is a type-I trans-membrane protein which is cleaved by several different membrane-associated proteases. The first cleavage of APP occurs extracellularly by one of two proteases, alpha-secretase or beta-secretase. Beta-secretase or BACE1 (beta-site APP-cleaving enzyme) is a type-I

transmembrane protein containing an aspartyl protease activity (described in detail below). Alpha secretase is a metalloprotease whose activity is most likely to be provided by one or a combination of the proteins ADAM10 and ADAM17. Following either the beta or alpha cleavage of APP, the final cleavage event occurs within the membrane and is carried out by a protein complex called gamma secretase. It is the combination of the beta and gamma secretase activities that results in the liberation of the Abeta peptides of 40 and 42 residues (there are also lower levels of other forms) from the APP and ultimately the formation of the amyloid plaques responsible for the pathology of Alzheimer's disease. It is believed that the Abeta-42 peptide is the most critical Abeta species, because it shows the most pronounced neurotoxicity, and can aggregate easily, thus forming a nucleus for the aggregation of other Abeta peptides, such as the Abeta-40 which is typically produced at higher levels than the other species.

The TAP-technology is particularly successful in the elucidation of membrane protein complexes. These multiprotein complexes form the core of the APP processing pathway and are not amenable to other techniques. Known proteins with an important functional role in APP processing were analysed with The applicant's technology to comprehensively chart the dynamic protein interactions that contribute to Abeta production. Selected novel targets are subsequently validated using cellular or biochemical assays. Moreover, purified multi-protein complexes (e.g. beta- or gamma-secretase) do represent defined functional molecular machines, which are used to evaluate the mechanism of known compounds and for the optimisation of leads.

### Presenilins

Presenilins 1 and 2 (PS1 and PS2) are integral membrane proteins which are localised in the endoplasmic reticulum, the Golgi and also at the cell surface [ Kovacs, D.M., et al., Alzheimer-associated presenilins 1 and 2: neuronal expression in brain and localization to intracellular membranes in mammalian cells. Nat Med, 1996. 2(2): p. 224-9]. They are predominantly found as a heterodimers of the NTF and CTF endoproteolytic fragments. The protease that cleaves presenilins (the "presenilinase") is not known, it is likely that the process is autocatalytic, also the functional significance of PS (auto)proteolysis is unclear.

Presenilins are involved in the proteolytical processing of Amyloid precursor protein (APP) [ De Strooper, B., et al, Nature, 1998. 391(6665): p. 387-902] and the Notch receptor [ De Strooper, B., et al., . Nature, 1999. 398(6727): p. 518-22., Ray, W.J., et al., . Proc Natl Acad Sci USA, 1999. 96(6): p. 3263-8.]. In addition, Presenilins are associated with the cell-adhesion proteins alpha and beta-catenin, N-cadherin, and E-cadherin [ Georgakopoulos, A., et al., Presenilin-1 forms complexes with the cadherin/catenin cell-cell adhesion system and is recruited to intercellular and synaptic contacts. Mol Cell, 1999. 4(6): p. 893-902] [ Zhang, Z., et al., . Nature, 1998. 395(6703): p. 698-702.] and other members of the armadillo family [ Yu, G., et al., . J Biol Chem, 1998. 273(26): p. 16470-5] [ Zhou, J., et al., . Neuroreport, 1997. 8(8): p. 2085-90] [ Levesque, G., et al., . J Neurochem, 1999. 72(3): p. 999-1008.] [1 Tanahashi, H. and T. Tabira, . Neuroreport, 1999. 10(3): p. 563-8.

]APP processing by Presenilins is through their effects on gamma-secretase which cleaves APP, generating the C-terminus of the A-beta peptide. PS1 associates with the C83 and C99 processed C-terminal fragments of APP [1 Xia, W., et al., . Proc Natl Acad Sci USA, 1997. 94(15): p. 8208-13.], Nicastrin [1 Yu, G., et al., . Nature, 2000. 407(6800): p. 48-54] and Pen-2 [1 Francis, R., et al. Dev Cell, 2002. 3(1): p. 85-97]. Aph-1 [1 Francis, R., et al., . Dev Cell, 2002. 3(1): p. 85-97] [1 Goutte, C., et al. Proc Natl Acad Sci U S A, 2002. 99(2): p. 775-9.] is required in Presenilin processing. It is not clear whether Presenilins regulate gamma-secretase activity directly or whether they are protease enzymes themselves Kopan, R. and A. Goate, . Genes Dev, 2000. 14(22): p. 2799-806. The gamma secretase activity could comprise a multimeric complex of these proteins [1 Yu, G., et al., . Nature, 2000. 407(6800): p. 48-54] [ Esler, W.P., et al., . Proc Natl Acad Sci U S A, 2002. 99(5): p. 2720-5.] but it is not known how the relationship between these proteins affects secretase activity.

Familial Alzheimer's disease (FAD) patients carry mutations in the presenilin proteins (PS1; PS2) or in APP. These mutations result in increased production of A-beta42 [1 Citron, M., et al., . Nat Med, 1997. 3(1): p. 67-72.] which is the main component of cerebral plaques in FAD [ Jarrett, J.T., E.P. Berger, and P.T. Lansbury, Jr., Biochemistry, 1993. 32(18): p. 4693-7.]

Understanding the composition of the gamma-secretase complex, the relationship between its component parts and its regulation are important in the design of drugs for use in Alzheimer's disease patients.

### **Nicastrin**

Nicastrin is a type 1 trans-membrane glycoprotein with a conserved transmembrane domain and DYIGS motif [1 Yu, G., et al., *Nature*, 2000. 407(6800): p. 48-54] which is constitutively expressed in neural cell lines [Satoh, J. and Y. Kuroda, *Neuropathology*, 2001. 21(2): p. 115-22.]. Biochemical studies have shown that Nicastrin binds to Presenilins 1 and 2, C-terminal derivatives of APP [ Yu, G., et al., *Nature*, 2000. 407(6800): p. 48-54.], membrane-tethered forms of Notch [2 Chen, F., et al.. *Nat Cell Biol*, 2001. 3(8): p. 751-4.] and that it is a member of the gamma-secretase complex along with PS1 and PS2 [16]. Gamma secretase activity is involved in the cleavage of both Notch and APP. It has been shown that Nicastrin is required for the intra-membrane cleavage of Notch [ Lopez-Schier, H. and D. St Johnston, . *Dev Cell*, 2002. 2(1): p. 79-89.] and APP [ Chung, H.M. and G. Struhl,. *Nat Cell Biol*, 2001. 3(12): p. 1129-32], it may also have a role in post-translational stabilisation of Presenilin [ Hu, Y., Y. Ye, and M.E. Fortini, . *Dev Cell*, 2002. 2(1): p. 69-78].

Aph-1 [ Goutte, C., et al., *Proc Natl Acad Sci U S A*, 2002. 99(2): p. 775-9] and Pen-2 [ Francis, R., et al., *Dev Cell*, 2002. 3(1): p. 85-97.] were cloned recently in a screen for presenilin enhancers ("pen") in *C. elegans* and shown to interact genetically with Aph-2 (Nicastrin). Defects in Aph-1 affect Notch signalling and Nicastrin localisation [ Goutte, C., et al., *Proc Natl Acad Sci U S A*, 2002. 99(2): p. 775-9.]. Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins. Francis et al. [ Francis, R., et al., . *Dev Cell*, 2002. 3(1): p. 85-97] cloned the putative human orthologues of these genes, Aph-1a, Aph-1b and Pen-2, and recently Lee et al. [24] also cloned the human Aph-1 cDNAs.

The exact components of the gamma-secretase complex are not known but these two novel proteins could be components of or accessory factors to the complex and may interact together directly with Presenilin or with a Presenilin/Nicastrin complex. Nicastrin is therefore a member of the active gamma-secretase complex and there is recent evidence that it is the fully glycosylated form of the protein which is important in this complex. ( Leem, J.Y., et al., . *J Biol Chem*, 2002. 9: p. 19236-40, Tomita, T., et al., . *FEBS Lett*, 2002. 520(1-3): p. 117-21, Edbauer, D., et al., . *Proc Natl Acad Sci U S A*, 2002. 99(13): p. 8666-71, Yang, D.S., et al., . *J Biol Chem*, 2002. 277(31): p. 28135-42., Kimberly, W.T., et al., *J Biol Chem*, 2002. 277: p. 35113-7. ]

### Aph-1

Goutte et al. [ Goutte, C., et al., Proc Natl Acad Sci U S A, 2002. 99(2): p. 775-9] cloned aph-1 from *C. elegans*. Aph-1 encodes a novel conserved membrane protein with seven hydrophobic regions which are predicted to be membrane spanning. It has a 40 amino acid hydrophilic tail. *C. elegans* aph1 mutants have a phenotype which is indicative of a defect in Notch signalling. In these mutants, Aph-2 (Nicastrin) localisation is altered from being at the cell surface to being in the cytoplasm, concentrated around the nucleus. In *C. elegans*, Aph-1 interacts genetically with Aph-2 (Nicastrin) and Sel-12 (one of the *C. elegans* Presenilin genes) [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97].

There are Human, Mouse, Drosophila Aph-1 homologues which are potential orthologues. Recently, the human Aph-1 homologues, hAph-1a and hAph-1b have been cloned [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97., Lee, S.F., et al., J Biol Chem, 2002. 23: p. 23.]. Aph-1a, the hypothetical CGI-78 protein, and Sambiasin-1 isolated by the applicant are all products of the same gene. Francis et al [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97.] showed that Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins in cultured Drosophila cells.

Lee et al. [ Lee, S.F., et al. J Biol Chem, 2002. 23: p. 23.] cloned two splice variants of Aph-1a called Aph-1aS and Aph-1aL and Aph-1b. They have shown that mammalian Aph-1aL associates with Nicastrin and PS1 NTF/CTF heterodimers and with PS2 and Nicastrin in cultured cells and that endogenous Aph1aL associates with Nicastrin and PS1 in rat brain. Inhibition of the expression of Aph1a reduces the expression of both PS1 and PS2 but not Nicastrin and results in the accumulation of gamma-secretase substrates and the reduction of AbetaAph1a was also shown to be required for Notch cleavage.

Aph-1 may have a role in the maturation and trafficking of Nicastrin but it is necessary for gamma-secretase function and may be a member of the gamma-secretase complex.

### Pen-2

Francis et al. [ Francis, R., et al., Dev Cell, 2002. 3(1): p. 85-97.] isolated pen-1 and pen-2 as two presenilin enhancer genes in a genetic screen in *C. elegans*. Pen-1 is identical to Aph-1 [ Goutte, C., et al., Proc Natl Acad Sci U S A, 2002. 99(2): p. 775-9.].

Pen-2 has two transmembrane domains and is thought to be a polytopic integral membrane protein. This group cloned the human homologues of Aph-1 and Pen-2. In *C. elegans*, Aph-1 and Pen-2 interact genetically with Aph-2 (Nicastrin) but not with each other. Hop-1 and Sel-12 are the *C.elegans* presenilin genes. Aph-2 interacts with Hop-1 whereas Aph-1 and Pen-2 interact with Sel-12 [ Francis, R., et al. Dev Cell, 2002. 3(1): p. 85-97].

Pen-2 associates with PS1, PS2 and Nicastrin in mammalian cells and Aph-1 and Pen-2 are required for Notch cleavage, gamma-secretase activity and the accumulation of processed Presenilins in cultured *Drosophila* cells [ Francis, R., et al., . Dev Cell, 2002. 3(1): p. 85-97].

Nicastrin maturation is affected by the levels of PS1 and Pen-2. Loss of PS1 or a reduction in expression of Nicastrin reduces Pen-2 protein levels and a reduction in expression of Pen-2 decreases levels of both PS1, PS2 proteins. In addition, reducing the expression of Pen-2 by RNAi reduces the level of the PS1 complex [ Steiner, H., et al., J Biol Chem, 2002: p. 39062-5]. These data suggest that Pen-2 is either a component of or regulates the assembly of the PS1 complex and that the expression of these proteins is co-ordinately regulated.

#### **BACE1 (beta-secretase)**

Vassar et al. [ Vassar, R., et al., Beta-secretase cleavage of Alzheimer's amyloid precursor protein by the transmembrane aspartic protease BACE. Science, 1999. 286(5440): p. 735-41.] cloned a transmembrane aspartic protease that had the characteristics of the postulated beta-secretase of APP. Three other groups also cloned BACE1 using different approaches. BACE1 knockout mice have a normal phenotype, suggesting that therapeutic inhibition of BACE1 for AD may be free of mechanism-based toxicity. BACE1 -/- mice who are also homozygous for an amyloid precursor protein transgene lack brain beta-amyloid and beta-secretase-cleaved APP C-terminal fragments. [ Roberds, S.L., et al., BACE knockout mice are healthy despite lacking the primary beta-secretase activity in brain: implications for Alzheimer's disease therapeutics. Hum Mol Genet, 2001. 10(12): p. 1317-24.

]. Brain and primary cortical cultures from BACE1 knockout mice showed no detectable beta-secretase activity, and primary cortical cultures from BACE knockout mice produced much less amyloid-beta from APP. This suggests that BACE1, rather than its parologue BACE2, is the main beta-secretase for APP.

BACE1 is a protein of 501 amino acids containing a 21-aa signal peptide followed by a proprotein domain spanning aa 22 to 45. There are alternatively spliced forms, BACE-I-457 and BACE-I-476. The luminal domain of the mature protein is followed by one predicted transmembrane domain and a short cytosolic C-terminal tail of 24 aa. BACE1 is predicted to be a type 1 transmembrane protein with the active site on the luminal side of the membrane, where beta-secretase cleaves APP and possibly other yet unidentified substrates. BACE1 mRNA in rat brain is present at higher levels in neurons than in glia, supporting that neurons are the primary source of the extracellular A-beta deposited in plaques. Sequence and mass spectrometry analyses showed that asn153, asn172, asn223, and asn354 of the BACE1 ectodomain are N-glycosylation sites. In addition, the ectodomain contains 6 cys residues that form disulfide bridges between positions 216 and 420, 278 and 443, and 330 and 380. The C-terminal domain of BACE1 contains a dileucine motif (LL499/500) that can potentially regulate its trafficking and endocytosis, and an adjacent serine, which is a casein kinase 1 phosphorylation site (S498) [ Huse, J.T., et al., Maturation and endosomal targeting of beta-site amyloid precursor protein-cleaving enzyme. The Alzheimer's disease beta-secretase. *J Biol Chem*, 2000. 275(43): p. 33729-37.

]. The propeptide is predominantly cleaved from BACE1 by furin [ Bennett, B.D., et al., A furin-like convertase mediates propeptide cleavage of BACE, the Alzheimer's beta -secretase. *J Biol Chem*, 2000. 275(48): p. 37712-7.]. In cells expressing wild or Swedish mutant APP, transient overexpression of BACE1 decreased alpha-secretase cleavage and increased beta-secretase activity at the known beta-secretase positions, asp1 and glu11. Although BACE1 is clearly a key enzyme required for the processing of APP into Ab, other potential substrates and functions of BACE1 are unknown. Also, no BACE1 interacting proteins with regulatory or modulatory functions have been described. Proteins that activate BACE1 activity would form suitable intervention points for Alzheimer's disease therapy. In addition, proteins that inhibit BACE1, like substrates or pseudosubstrates, could also provide suitable means of intervention e.g. as proteins therapeutics.

### APP

APP is the precursor of Abeta, a peptide which forms the principal component of Alzheimer disease (AD) senile plaques [ Masters, C.L., et al., *Proc Natl Acad Sci U S A*, 1985. 82(12): p. 4245-9.] Masters et al. purified the cerebral amyloid protein that forms

the plaque core in AD and Down syndrome. Van Nostrand et al. [ Van Nostrand, W.E., et al.,. Nature, 1989. 341(6242): p. 546-9.] presented evidence that nixin-II, a protease inhibitor that is synthesized and secreted by extravascular cells, is identical to APP. Multhaup et al. [ Multhaup, G., et al.,. Science, 1996. 271(5254): p. 1406-9.] demonstrated that APP is involved in copper reduction. They postulated that copper-mediated toxicity may contribute to neurodegeneration in AD, possibly by increased production of hydroxyl radicals. Yan et al. [ Yan, S.D., et al., . Nature, 1996. 382(6593): p. 685-91.] reported that the receptor for advanced glycation end products RAGE is a receptor for the  $\alpha$ -beta peptide and that expression of this receptor increases in AD. Expression of RAGE is particularly increased in neurons close to deposits of amyloid beta peptide and to neurofibrillary tangles. Kaneko et al. [ Kaneko, I., et al.,. J Neurochem, 1995. 65(6): p. 2585-93.] demonstrated that nanomolar concentrations of various synthetic beta amyloids specifically impaired mitochondrial succinate dehydrogenase, and speculated that one of the primary targets of beta amyloids is the mitochondrial electron transport chain.

Several missense mutations in the APP gene have been identified that result in early-onset AD: the Swedish APP670/671 double mutation; 3 different mutations at codon 717: the London APP717 mutation, V717I, V717F, and V717G; and the Florida APP716 mutation (Reviewed by Bertram and Tanzi [ Bertram, L. and R.E. Tanzi,. J Mol Neurosci, 2001. 17(2): p. 127-36.]). Most of these AD-related mutations involve amino acid changes near the beta- and gamma-secretase cleavage sites. Two other missense mutations in the APP gene are located within A-beta near the alpha-secretase cleavage site: the Flemish APP692 mutation, which is associated with cerebral hemorrhage due to congophilic amyloid angiopathy or with early-onset AD with onset age in the mid-forties; and the Dutch APP693 mutation. Almost all AD-linked mutations do elevate secretion of A-beta-42, however, APP693 does not. [ De Jonghe, C., et al.. Neurobiol Dis, 1998. 5(4): p. 281-6.]

Cao and Sudhof [ Cao, X. and T.C. Sudhof,. Science, 2001. 293(5527): p. 115-20] demonstrated that the cytoplasmic tail of APP forms a complex with the nuclear adaptor protein Fe65 and the histone acetyltransferase TIP60. This complex stimulates transcription via heterologous Gal4 or LexA DNA binding domains, suggesting that release of the cytoplasmic tail of APP by gamma-cleavage may function in gene expression. The complex could modify expression of genes that function in inflammation

[ Baek, S.H., et al.,. Cell, 2002. 110(1): p. 55-67] or apoptosis [ Kinoshita, A., et al.,. J Biol Chem, 2002. 277(32): p. 28530-6.]

Weggen et al. [ Weggen, S., et al.,. Nature, 2001. 414(6860): p. 212-6.] reported that the nonsteroidal antiinflammatory drugs ibuprofen, indomethacin, and sulindac can decrease the levels of high amyloidogenic amyloid-beta-42 peptide produced from a variety of cultured cells by as much as 80%. This effect was not seen in all NSAIDs and seemed not to be mediated by inhibition of cyclooxygenase (Cox) activity. Weggen et al. (2001) also demonstrated that short-term administration of ibuprofen to mice that produce APP lowered their brain levels of amyloid-beta-42. In cultured cells, the decrease in amyloid-beta-42 secretion was accompanied by an increase in the amyloid-beta(1-38) isoform, indicating that NSAIDs subtly alter gamma-secretase activity without significantly perturbing other APP processing pathways or Notch cleavage.

Proteins and other factors that regulate APP processing, and especially those that influence levels of Abeta-42 versus other Abeta species, form important potential targets in AD therapy.

### Tau

Neurofibrillary tangles (NFT), intraneuronal tau protein deposits, are hallmarks of several neurodegenerative disorders such as Alzheimer's and Pick's disease, frontotemporal dementia, cortico-basal degeneration and progressive supranuclear palsy.

The seven tau isoforms are all products of a single gene. Alternative splicing gives rise to six mRNA species differentially expressed in the CNS, depending on stage of neuronal maturation and neuron type. Tau is found mainly in the axon whereas a related protein, MAP2, is mainly found in dendrites.

Tau and MAP2 are microtubule-associated proteins (MAPs) which coassemble with microtubules and colocalise with microtubules in cells. Tau is a nonstructured molecule with a microtubule binding site containing 3 or 4 characteristic amino acid repeat in its carboxyl-terminal half. Alonso et al. [ Alonso, A.C., I. Grundke-Iqbali, and K. Iqbali,. Nat Med, 1996. 2(7): p. 783-7.] noted that in the brains of AD patients the neuronal cytoskeleton is progressively disrupted and replaced by tangles of paired helical filaments (PHFs), and that PHFs are composed mainly of hyperphosphorylated forms of tau. They demonstrated that in solution normal tau associated with the hyperphosphorylated AD P-tau to form large tangles of filaments. They also

demonstrated that dephosphorylation with alkaline phosphatase abolished the ability of AD P-tau to aggregate in vitro. In a form of autosomal dominant inherited dementia known as FTDP17 or Pick disease, the tau gene carries missense mutations or mutations in the 5'- splice site of exon 10, which results in increased levels of tau isoforms with 4 microtubule-binding repeats. These mutations lead to tau molecules that show reduced affinity for microtubules or are more prone to self aggregation.

Proteins and other factors that influence the affinity of tau protein for microtubules, and moreover, influence the aggregation of tau, which is probably mediated by phosphorylation and dephosphorylation events, are important potential targets in AD therapy.

### **X11beta**

X11beta/Mint-2 is a neuronal adaptor protein that is believed to be involved in signal transduction processes. It is also regarded as a putative vesicular trafficking protein in the brain that can form a complex with the potential to couple synaptic vesicle exocytosis to neuronal cell adhesion [ Biederer, T. and T.C. Sudhof., J Biol Chem, 2000. 275(51): p. 39803-6.].

X11beta interacts with the Alzheimer's disease amyloid precursor protein (APP) [ McLoughlin, D.M. and C.C. Miller., FEBS Lett, 1996. 397(2-3): p. 197-200.]. Acting synergistically with Munc18a [ Ho, C.S., et al., J Biol Chem, 2002. 277(30): p. 27021-8.], X11beta stabilises APP and inhibits production of proteolytic APP fragments including the A beta peptide that is deposited in the brains of Alzheimer's disease patients [ Sastre, M., R.S. Turner, and E. Levy., J Biol Chem, 1998. 273(35): p. 22351-7.].

Via a mechanism that depends on its PDZ domain (yet has otherwise not been characterized), X11beta potently inhibits transactivation by an APP-Gal4/VP16 fusion protein [ Ho, C.S., et al., J Biol Chem, 2002. 277(30): p. 27021-8.]. Besides interacting with APP, X11beta binds to the C-terminus of presenilin1, although not as strongly as does X11alpha [ Ho, C.S., et al., J Biol Chem, 2002. 277(30): p. 27021-8.]. In addition, X11beta has been reported to interact with XB51 [ Lee, D.S., et al., J Biol Chem, 2000. 275(30): p. 23134-8.], but the functional significance of this interaction is unknown.

In Drosophila, dX11beta overexpression in eye imaginal disks causes disruption of compound eye morphology due to enhanced apoptosis of neuronal cells [ Hase, M., et al., J Neurochem, 2002. 81(6): p. 1223-32.]. X11beta has been shown to bind to NF-KappaB-p65 through its PDZ domain. This interaction has been implicated in NF-

KappaB-dependent Abeta42 production [ Tomita, S., et al., J Biol Chem, 2000. 275(17): p. 13056-60.].

Elucidation of X11beta complex composition and regulation might therefore help develop novel ways of therapeutic intervention in Alzheimer's disease and inflammation.

### BACE2

BACE2 is a glycosylated transmembrane protein of the aspartic protease family, constitutes the only paralog of BACE1, and was mapped to the Down's critical region of human chromosome ( Acquati, F., Accarino, M., Nucci, C., Fumagalli, P., Jovine, L., Ottolenghi, S., and Taramelli, R. (2000) FEBS Lett 468, 59-64, Solans, A., Estivill, X., and de La Luna, S. (2000) Cytogenet Cell Genet 89, 177-184, Farzan, M., Schnitzler, C. E., Vasilieva, N., Leung, D., and Choe, H. (2000) Proc Natl Acad Sci U S A 97, 9712-9717, Hussain, I., Powell, D. J., Howlett, D. R., Chapman, G. A., Gilmour, L., Murdock, P. R., Tew, D. G., Meek, T. D., Chapman, C., Schneider, K., Ratcliffe, S. J., Tattersall, D., Testa, T. T., Southan, C., Ryan, D. M., Simmons, D. L., Walsh, F. S., Dingwall, C., and Christie, G. (2000) Mol Cell Neurosci 16, 609-619). Both endoproteases share similar structural organization including a prodomain, a catalytic domain formed via DTG and DSG active site motifs, a single transmembrane domain, and a short C-terminal tail. BACE2 is expressed at low levels in most human peripheral tissues and at higher levels in colon, kidney, pancreas, placenta, prostate, stomach, and trachea. Human adult and fetal whole brain and most adult brain subregions express very low or undetectable levels of BACE2 mRNA ( Bennett, B. D., Babu-Khan, S., Loeloff, R., Louis, J. C., Curran, E., Citron, M., and Vassar, R. (2000) J Biol Chem 275, 20647-2065). BACE2 has a limited effect on the beta-secretase site but efficiently cleaves the sequences near the alpha-secretase site ( Yan, R., Munzner, J. B., Shuck, M. E., and Bienkowski, M. J. (2001) J Biol Chem 276, 34019-34027). BACE2 localizes in the endoplasmic reticulum, Golgi, trans-Golgi network, endosomes, and plasma membrane, and its cellular localization patterns depend on the presence of its transmembrane domain. BACE1 knockout mice are viable, possibly due to a redundancy in function with BACE2 ( Roberds, S. L., Anderson, J., Basi, G., Bienkowski, M. J., Branstetter, D. G., Chen, K. S., Freedman, S. B., Frigon, N. L., Games, D., Hu, K., Johnson-Wood, K., Kappenstein, K. E., Kawabe, T. T., Kola, I., Kuehn, R., Lee, M., Liu, W., Motter, R., Nichols, N. F., Power, M., Robertson, D. W., Schenk, D., Schoor, M., Shopp, G. M., Shuck, M. E., Sinha, S.,

Svensson, K. A., Tatsuno, G., Tintrup, H., Wijsman, J., Wright, S., and McConlogue, L. (2001) *Hum Mol Genet* 10, 1317-1324).

Protein complexes involving BACE2 are of potential therapeutic value in AD therapy. The determination of the nature of the proteins interacting with and potentially regulating BACE1 but not BACE2 will constitute suitable therapeutic targets.

### Dab1

We have used mouse DAB1 because human Dab1 has not been cloned. Mutation in disabled-1 (Dab1) resemble mutations in reelin (Reln) by causing abnormalities in laminar structures throughout the brain and ataxia in reeler and scrambler mice ( Rice, D. S., Sheldon, M., D'Arcangelo, G., Nakajima, K., Goldowitz, D., and Curran, T. (1998) *Development* 125, 3719-3729). However, Reln and Dab1 are distinct in their molecular properties. Reln is a large extracellular protein secreted in the forebrain and the cerebellum. Dab1 is a cytoplasmic adapter protein that functions in phosphorylation-dependent intracellular signal transduction. It is suggested that Dab1 functions downstream of Reln in a signaling pathway that controls cell positioning in the developing brain ( Rice, D. S., Sheldon, M., D'Arcangelo, G., Nakajima, K., Goldowitz, D., and Curran, T. (1998) *Development* 125, 3719-3729). Reelin stimulates tyrosine kinases of the src family by a mechanism involving Dab1 ( Arnaud, L., Ballif, B. A., Forster, E., and Cooper, J. A. (2003) *Curr Biol* 13, 9-17

). DAB1 has also been reported to interact with APP ( Trommsdorff, M., Borg, J. P., Margolis, B., and Herz, J. (1998) *Journal of Biological Chemistry* 273, 33556-33560) and with the cytoplasmic tails of LRP and LDL receptor (18). It was shown that Reln binds directly and specifically to the extracellular domains of VLDLR and ApoER2. Blockade of VLDLR and ApoER2 ligand binding correlated with loss of Reelin-induced Dab1 tyrosine phosphorylation. Mice lacking either Reln or VLDLR and ApoER2 show an increase in the phosphorylation level of tau proteins suggesting that Reln acts via Vldlr and ApoER2 to regulate Dab1 tyrosine phosphorylation and tau function in neurons ( Hiesberger, T., Trommsdorff, M., Howell, B. W., Goffinet, A., Mumby, M. C., Cooper, J. A., and Herz, J. (1999) *Neuron* 24, 481-489.). The functional role of the binding of Dab1 to the C-termini of APP, APLP1 and APLP2 has not been elucidated.

The protein complex around DAB1 is of high potential therapeutic interest for AD and related neurodegenerative diseases because it could provide further links of amyloid

pathology to downstream tangle pathology, and provide targets for the therapeutic modulation of the intracellular pathways leading to tau phosphorylation, tangle buildup, and neuronal death in AD.

### Fe65L2

Fe65 proteins are ligands of the cytoplasmic domain of APP ( Fiore, F., Zambrano, N., Minopoli, G., Donini, V., Duilio, A., and Russo, T. (1995) J Biol Chem 270, 30853-30856). The fe65 gene has two paralogues, Fe65L1 ( Guenette, S. Y., Chen, J., Jondro, P. D., and Tanzi, R. E. (1996) Proc Natl Acad Sci U S A 93, 10832-10837) and Fe65L2 ( Duilio, A., Faraonio, R., Minopoli, G., Zambrano, N., and Russo, T. (1998) Biochem J 330 ( Pt 1), 513-519). Fe65L2 encodes a protein of approx. 50 kDa which is expressed predominantly in brain and testis ( Tanahashi, H., Asada, T., and Tabira, T. (2002) Ann Neurol 52, 691-693). The three paralogues of the Fe65 protein family share three regions corresponding to the protein-protein interaction domains; the WW domain and the two PTB domains, whereas the remaining sequences are poorly related. Like Fe65, Fe65L1 and Fe65L2 genes encode two different protein isoforms, derived from the alternative splicing of a six nucleotide exon within the N-terminal PTB domain, in the presence or absence of two acidic/basic amino acids. Fe65 proteins have been found to translocate into the nucleus and to prevent the activation of the thymidylate synthase gene promoter induced by the transcription factor CP2 by an unknown mechanism ( Bruni, P., Minopoli, G., Brancaccio, T., Napolitano, M., Faraonio, R., Zambrano, N., Hansen, U., and Russo, T. (2002) J Biol Chem 277, 35481-35488).

Fe65L2 is able to interact, both in vitro and in vivo, with the intracellular domain of APP. Fe65 and Fe65L2 interact with APP, APLP1 and APLP2 with different efficiencies ( Duilio, A., Faraonio, R., Minopoli, G., Zambrano, N., and Russo, T. (1998) Biochem J 330 ( Pt 1), 513-519). Overexpression of Fe65L2 was reported to increase secretion of Abeta 1-40 and Abeta 1-42, however the molecular mechanism of this amyloidogenic effect is unknown. A c954C-->T polymorphism in the Fe65L2 gene is possibly associated with early-onset Alzheimer's disease (21). Fe65 proteins have been found to translocate into the nucleus and to prevent the activation of the thymidylate synthase gene promoter induced by the transcription factor CP2 by an unknown mechanism ( Bruni, P., Minopoli, G., Brancaccio, T., Napolitano, M., Faraonio, R., Zambrano, N., Hansen, U., and Russo,

T. (2002) J Biol Chem 277, 35481-35488). There are no interactors of Fe65L2 known that are not also found with Fe65.

The protein complex around Fe65L2 is of high potential therapeutic interest for AD and related neurodegenerative diseases because membrane-associated, cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) with adaptor proteins regulate APP stability and turnover, nuclear translocation, and its transcriptional function, which are all potential targets for therapeutic intervention.

### **JIP1 (MAPK8IP1)**

The JIP proteins (40) function by scaffolding components of a MAP kinase module (including MLK, MKK7, and JNK) and facilitate signal transmission by the protein kinase cascade ( Yasuda, J., Whitmarsh, A. J., Cavanagh, J., Sharma, M., and Davis, R. J. (1999) Mol Cell Biol 19, 7245-7254).

Waeber et al. evaluated the role of JIP1 in beta-cells and proposed JIP-1 as a candidate gene for human diabetes. In one family a JIP1 missense mutation S59N segregated with diabetes and thus JIP1 represents a candidate susceptibility gene for type 2 diabetes ( Waeber, G., Delplanque, J., Bonny, C., Mooser, V., Steinmann, M., Widmann, C., Maillard, A., Miklossy, J., Dina, C., Hani, E. H., Vionnet, N., Nicod, P., Boutin, P., and Froguel, P. (2000) Nat Genet 24, 291-295).

Two groups presented evidence for an interaction of JIP1b with the cytoplasmic tail of APP ( Scheinfeld, M. H., Matsuda, S., and D'Adamio, L. (2003) Proc Natl Acad Sci U S A 100, 1729-1734, Scheinfeld, M. H., Roncarati, R., Vito, P., Lopez, P. A., Abdallah, M., and D'Adamio, L. (2002) J Biol Chem 277, 3767-3775., Matsuda, S., Yasukawa, T., Homma, Y., Ito, Y., Niikura, T., Hiraki, T., Hirai, S., Ohno, S., Kita, Y., Kawasumi, M., Kouyama, K., Yamamoto, T., Kyriakis, J. M., and Nishimoto, I. (2001) J Neurosci 21, 6597-6607.). Another group reported a mutual relationship of the expression levels of JIP1 and alpha synuclein in cultured neurons ( Hashimoto, M., Hsu, L. J., Rockenstein, E., Takenouchi, T., Mallory, M., and Masliah, E. (2002) J Biol Chem 277, 11465-11472.). Over-expression of JIP1 has been reported to stabilize immature APP and to suppress the production of an intracellular carboxyl-terminal fragment of APP (APP intracellular domain (AICD)), and the secretion of peptides A-beta 1-40 and A-beta 1-42, the predominant constituents of amyloid plaques in Alzheimer's disease. The mechanism of JIP1's amyloidogenic function is unknown. JIP1 and related proteins JIP2 and JIP3 bind

to the C-terminus of kinesin light chain suggesting that a JIP1-containing protein complex might be involved in APP trafficking ( Inomata, H., Nakamura, Y., Hayakawa, A., Takata, H., Suzuki, T., Miyazawa, K., and Kitamura, N. (2003) *J Biol Chem*, Verhey, K. J., Meyer, D., Deehan, R., Blenis, J., Schnapp, B. J., Rapoport, T. A., and Margolis, B. (2001) *J Cell Biol* 152, 959-970).

The protein complex around JIP1 is of high potential therapeutic interest for AD and related neurodegenerative diseases because membrane-associated, cytoplasmic and nuclear complexes of the APP intracellular domain (AICD) with adaptor proteins regulate APP stability and turnover, nuclear translocation, and its transcriptional function, which are all potential targets for therapeutic intervention.

### FKRP

Brockington et al. identified the fukutin-related protein gene (FKRP) by database screening using the mouse fukutin sequence and cloned fukutin-related protein (FKRP) by a combination of EST assembly, RT-PCR, and RACE ( Brockington, M., Blake, D. J., Prandini, P., Brown, S. C., Torelli, S., Benson, M. A., Ponting, C. P., Estournet, B., Romero, N. B., Mercuri, E., Voit, T., Sewry, C. A., Guicheney, P., and Muntoni, F. (2001) *Am J Hum Genet* 69, 1198-1209) . The cDNA encodes a 495-amino acid protein with a molecular organization similar to several Golgi-resident glycosyltransferases. Northern blot analysis detected a 4.0-kb FKRP transcript expressed predominantly in skeletal muscle, placenta, and heart and relatively weakly in other tissues.

FKRP mutations are found in families with severe and early-onset phenotypes of congenital muscular dystrophies (CMD). Structural brain defects, with or without mental retardation, are additional features of CMD. A variable reduction of alpha-dystroglycan expression was observed in the skeletal muscle biopsy of all individuals studied. In addition, several cases showed a deficiency of laminin 2 ( Brockington, M., Blake, D. J., Prandini, P., Brown, S. C., Torelli, S., Benson, M. A., Ponting, C. P., Estournet, B., Romero, N. B., Mercuri, E., Voit, T., Sewry, C. A., Guicheney, P., and Muntoni, F. (2001) *Am J Hum Genet* 69, 1198-1209, Brockington, M., Yuva, Y., Prandini, P., Brown, S. C., Torelli, S., Benson, M. A., Herrmann, R., Anderson, L. V., Bashir, R., Burgunder, J. M., Fallet, S., Romero, N., Fardeau, M., Straub, V., Storey, G., Pollitt, C., Richard, I., Sewry, C. A., Bushby, K., Voit, T., Blake, D. J., and Muntoni, F. (2001) *Hum Mol Genet* 10, 2851-2859).

FKRP and fukutin are Golgi-resident proteins and FKRP is required for the post-translational modification of dystroglycan ( Esapa, C. T., Benson, M. A., Schroder, J. E., Martin-Rendon, E., Brockington, M., Brown, S. C., Muntoni, F., Kroger, S., and Blake, D. J. (2002) *Hum Mol Genet* 11, 3319-3331).

FKRP is a novel interactor of PS1. Since exit of presenilins and the active gamma-secretase complex from the ER is critical for gamma-secretase function (52), FKRP and associated proteins may play a role in regulating gamma-secretase activity and/or trafficking, allowing access to APP. Interfering with FTRP and associated proteins may be a therapeutic strategy for the treatment of AD.

### **Protein Tyrosine Kinase 7 (PTK7)**

PTK7, also referred to as colon carcinoma kinase 4 (CCK4), is an immunoglobulin superfamily transmembrane glycoprotein related to chicken KLG and *D. melanogaster* off-track. The gene has been mapped to human chromosome 6p21.1-->p12.2 by fluorescence in situ hybridization (Banga et al., 1997, *Cytogenet Cell Genet.* 1997;76(1-2):43-4).

PTK7, several splicing variants of which exist in human tissues, differs from the receptor tyrosine kinase consensus sequence in several positions, suggesting that the protein be catalytically inactive (Mossie et al., 1995, *Oncogene.* 1995 Nov 16;11(10):2179-84.). PTK7 is expressed in multiple human tissues, but its function is unknown. However, its similarity to the *D. melanogaster* transmembrane protein Off-track/Dtrk, which serves as a coreceptor of plexin A for semaphorins Sema 1A (Winberg et al., *Neuron.* 2001 Oct 11;32(1):53-62) and Sema 6D (Toyofuku et al., *Genes Dev.* 2004 Feb 15;18(4):435-47.), suggests that PTK7 might act as a coreceptor of a plexin-like protein. In the CNS, PTK7 might therefore play a role in maintenance of neuronal connectivity.

### **Glycogen Synthase Kinase 3a (GSK3a)**

GSK3a is a serine/threonine kinase that has been implicated in regulation of APP processing: RNA interference with GSK3a expression attenuates secretion of Abeta peptides (Phiel et al., 2003). Moreover, millimolar concentrations of lithium inhibit Abeta production both in-vitro and in-vivo. It has been suggested that GSK3a be the target that mediates lithium action in this context (Phiel et al, *Nature.* 2003 May 22;423(6938):435-

9). Since lithium blocks APP cleavage at the gamma-secretase step without interfering with Notch processing, GSK3a might constitute a suitable target for therapeutic intervention in AD.

### Beta-Catenin (CtnnB1)

Beta-catenin is a key player in the Wnt signaling pathway during embryonic patterning and cell-fate determination. Beta-catenin-containing nuclear protein complexes facilitate transcription of a broad range of target genes. Consequently, dysregulation of the Wnt pathway in general and beta-catenin in particular has been implicated in the pathogenesis of various types of cancer. Beta-catenin function is therefore tightly regulated by various effector proteins (van Es et al., Curr Opin Genet Dev. 2003 Feb;13(1):28-33).

Presenilin 1 binds to beta-catenin (Yu et al., J Biol Chem. 1998 Jun 26;273(26):16470-5.) and acts as a negative regulator of Wnt/beta-catenin signaling. Presenilin 1, containing familial AD mutations, destabilizes beta-catenin and potentiate neuronal apoptosis (Zhang et al., Nature. 1998 Oct 15;395(6703):698-702.). It has recently been proposed that presenilin 1 serves as a scaffold that promotes Wnt-independent phosphorylation and subsequent attenuation of beta-catenin-dependent transcription (Kang et al., Cell. 2002 Sep 20;110(6):751-62.). Loss of presenilin 1, in turn, is associated with enhanced beta-catenin signaling and skin tumorigenesis (Xia et al., Proc Natl Acad Sci U S A. 2001 Sep 11;98(19):10863-8.).

### 3. SUMMARY OF THE INVENTION

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

1. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions;and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active

- derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
3. A protein complex comprising the proteins selected from the proteins in table 1, third column or a homologue thereof, or a variant thereof or functionally active fragments or functionally active derivatives of said proteins, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions; wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, but 1 to the number of proteins listed in table 1, fifth column of said complex, or a homologue or a variant thereof, or a functionally active fragment or functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins of said fifth column under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm

DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the biochemical activity as stated in table 3.
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No.1 (a) and at least one of said proteins, being selected from the second group of proteins according to No.1 (b).
14. Host cell, containing a vector comprising a construct of No. 13 or containing several vectors each comprising at least the nucleic acid encoding at least one protein selected from the first group of proteins according to No.1 (a) and the nucleic acid encoding at least one protein selected from the second group of proteins according to No.1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any of No.1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more containers the complex of any of No. 1 - 8, optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of a complex of any one of No. 1 - 8.
18. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
19. Array in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 17 is attached to a solid carrier.

20. A process for processing a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8.
22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders, preferentially for diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
23. A method for screening for a molecule that binds to the complex of any one of No. 1 - 8, comprising the following steps:
  - (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
24. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.

25. The method of No. 24, wherein the amount of said complex is determined.
26. The method of No. 25, wherein the activity of said complex is determined.
27. The method of No. 25, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
28. The method of No. 24, wherein the amount of the individual protein components of said complex are determined.
29. The method of No. 25, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
30. The method of any of No. 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

32. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 24 - 29 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
33. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.
34. The method of No. 33, wherein the amount of said complex is determined.
35. The method of No. 33, wherein the activity of said complex is determined.
36. The method of No. 35, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
37. The method of No. 33, wherein the amount of the individual protein components of said complex are determined.
38. The complex of any one of No. 1 - 8 or the antibody of fragment of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder

such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.
40. The method according to No. 39, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
41. The method according to No. 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
42. Complex of No. 1 - 8 and/or any of the proteins listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

### **3.1 DEFINITIONS**

The term "activity" as used herein, refers to the function of a molecule in its broadest sense. It generally includes, but is not limited to, biological, biochemical, physical or chemical functions of the molecule. It includes for example the enzymatic activity, the ability to interact with other molecules and ability to activate, facilitate, stabilize, inhibit, suppress or destabilize the function of other molecules, stability, ability to localize to certain subcellular locations. Where applicable, said term also relates to the function of a protein complex in its broadest sense.

The term "agonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, increases the amount of, or prolongs the

duration of, the activity of the complex. The stimulation may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Agonists may include proteins, nucleic acids, carbohydrates or any other organic or anorganic molecule or metals. Agonists also include a functional peptide or peptide fragment derived from a protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred activators are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 25%, at least 50%, at least 100%, at least, 200%, at least 500% or at least 1000% at a concentration of the activator  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ . Any combination of the above mentioned degrees of percentages and concentration may be used to define an agonist of the invention, with greater effect at lower concentrations being preferred.

The term "amount" as used herein and as applicable to the embodiment described relates to the amount of the particular protein or protein complex described, including the value of null, i.e. where no protein or protein complex described in that particular embodiment is present under the or any of the conditions which might be specified in that particular embodiment.

The term "animal" as used herein includes, but is not limited to mammals, preferably mammals such as cows, pigs, horses, mice, rats, cats, dogs, sheep, goats and most preferably humans. Other animals used in agriculture, such as chickens, ducks etc. are also included in the definition as used herein.

The term "animal" as used herein does not include humans if being used in the context of genetic alterations to the germline.

The term "antagonist" as used herein, means a molecule which modulates the formation of a protein complex or which, when bound to a complex or protein of the invention or a molecule in the protein complex, decreases the amount of, or the duration or level of activity of the complex. The effect may be direct or indirect, including effects on the expression of a gene encoding a member of the protein complex, or by a competitive or non-competitive mechanism. Antagonists may include proteins, including antibodies, nucleic acids, carbohydrates or any other organic or anorganic molecule or metals. Antagonists also include a functional peptide or peptide fragment derived from a

protein member of the complexes of the invention or a protein member itself of the complexes of the invention. Preferred antagonists are those which, when added to the complex and/or the protein of the invention under physiological conditions and/or in vitro assays, including diagnostic or prognostic assays, result in a change of the level of any of the activities of the protein complex and/or the proteins of the invention as exemplary illustrated above by at least 10%, at least 20%, at least 30%, at least 40% at least 50%, at least 60%, at least 70%, at least 80%, at least 90%, at least 95% or at least 99% at a concentration of the inhibitor of  $1\mu\text{g ml}^{-1}$ ,  $10\mu\text{g ml}^{-1}$ ,  $100\mu\text{g ml}^{-1}$ ,  $500\mu\text{g ml}^{-1}$ ,  $1\text{mg ml}^{-1}$ ,  $10\text{mg ml}^{-1}$  or  $100\text{mg ml}^{-1}$ .

Any combination of the above mentioned degrees of percentages and concentration may be used to define antagonist of the invention, with greater effect at lower concentrations being preferred.

The term "antibodies" as used herein, include include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library.

The term "binding" as used herein means a stable or transient association between two molecules, including electrostatic, hydrophobic, ionic and/or hydrogen-bond interaction under physiological conditions and/or conditions being used in diagnostic or prognostic method or process or procedure.

The term "carrier" as used herein refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional

binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

If not stated otherwise, the terms "complex" and "protein complex" are used interchangeably herein and refer to a complex of proteins that is able to perform one or more functions of the wild type protein complex. The protein complex may or may not include and/or be associated with other molecules such as nucleic acid, such as RNA or DNA, or lipids or further cofactors or moieties selected from a metal ions, hormones, second messengers, phosphate, sugars.

A "complex" of the invention may also be part of or a unit of a larger physiological protein assembly.

The term "component of the APP processing pathway" as used herein refers to a protein and/or protein complex which is involved in mediating APP processing in a cell. Components of the APP processing pathway include the following protein complexes as provided herein and components thereof:

BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastin-complex, Aph-1a, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex.

If not stated otherwise, the term "compound" as used herein are include but are not limited to peptides, nucleic acids, carbohydrates, natural product extract libraries organic molecules, preferentially small organic molecules, anorganic molecules, including but not limited to chemicals, metals and organometallic molecules.

The terms "derivatives" or "analogs of component proteins" or "variants" as used herein include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done

by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions. It means a protein which is the outcome of a modification of the naturally occurring protein, by amino acid substitutions, deletions and additions, respectively, which derivatives still exhibit the biological function of the naturally occurring protein although not necessarily to the same degree. The biological function of such proteins can e.g. be examined by suitable available in vitro assays as provided in the invention.

The term "functionally active" as used herein refers to a polypeptide, namely a fragment or derivative, having structural, regulatory, or biochemical functions of the protein according to the embodiment of which this polypeptide, namely fragment or derivative is related to.

The term "fragment" as used herein refers to a polypeptide of at least 10, 20, 30, 40 or 50 amino acids of the component protein according to the embodiment. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids.

The term "gene" as used herein refers to a nucleic acid comprising an open reading frame encoding a polypeptide of, if not stated otherwise, the present invention, including both exon and optionally intron sequences.

The terms "homologue" or "homologous gene products" as used herein mean a protein in another species, preferably mammals, which performs the same biological function as the a protein component of the complex further described herein. Such homologues are also termed "orthologous gene products". The algorithm for the detection of orthologue gene pairs from humans and mammals or other species uses the whole genome of these organisms. First, pairwise best hits are retrieved, using a full Smith-Waterman alignment of predicted proteins. To further improve reliability, these pairs are clustered with pairwise best hits involving *Drosophila melanogaster* and *C. elegans* proteins. Such analysis is given, e.g., in *Nature*, 2001, 409:860-921. The homologues of the proteins according to the invention can either be isolated based on the sequence homology of the genes encoding the proteins provided herein to the genes of other species by cloning the respective gene applying conventional technology and expressing the protein from such gene, or by isolating proteins of the other species by isolating the analogous complex according to the methods provided herein or to other suitable methods commonly known in the art.

The term "host cells" or, were applicable, "cells" or "hosts" as used herein is intended to be understood in a broadest sense and include, but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used. It is understood that this term not only refers to the particular subject cell but to the progeny or potential progeny of such a cell. Because certain modifications may occur in succeeding generations due to either mutation or environmental influences, such progeny may not, in fact, be identical to the parent cell, but are still included within the scope of the term as used herein.

The term "modification" as used herein refers to all modifications of a protein or protein complex of the invention including cleavage and addition or removal of a group.

The term "nucleic acid" as used herein refers to polynucleotides such as deoxyribonucleic acid (DNA), and, where appropriate, ribonucleic acid (RNA). They may also be polynucleotides which include within them synthetic or modified nucleotides. A number of different types of modification to polynucleotides are known in the art. These include methylphosphonate and phosphorothioate backbones, addition of acridine or polylysine chains at the 3' and/or 5' ends of the molecule. For the purposes of the present invention, it is to be understood that the polynucleotides described herein may be modified by any method available in the art. Such modifications may be carried out in order to enhance the *in vivo* activity or lifespan of polynucleotides of the invention. Polynucleotides according to the invention may be produced recombinantly, synthetically, or by any means available to those of skill in the art. They may also be cloned by standard techniques. The polynucleotides are typically provided in isolated and/or purified form. As applicable to the embodiment being described, they include both single stranded and double-stranded polynucleotides.

The term "percent identity", as used herein, means the number of identical residues as defined by an optimal alignment using the Smith-Waterman algorithm divided by the length of the overlap multiplied by 100. The alignment is performed by the search program (Pearson, 1991, Genomics 11:635-650) with the constraint to align the maximum of both sequences.

The terms "polypeptides" and "proteins" are, where applicable, used interchangeably herein. They may be chemically modified, e.g. post-translationally modified. For example, they may be glycosylated or comprise modified amino acid residues. They may also be modified by the addition of a signal sequence to promote their secretion from a cell where the polypeptide does not naturally contain such a sequence. They may be tagged with a tag. They may be tagged with different labels which may assist in identification of the proteins in a protein complex. Polypeptides/proteins for use in the invention may be in a substantially isolated form. It will be understood that the polypeptid/protein may be mixed with carriers or diluents which will not interfere with the intended purpose of the polypeptide and still be regarded as substantially isolated. A polypeptide/protein for use in the invention may also be in a substantially purified form, in which case it will generally comprise the polypeptide in a preparation in which more than 50%, e.g. more than 80%, 90%, 95% or 99%, by weight of the polypeptide in the preparation is a polypeptide of the invention.

"Target for therapeutic drug" means that the respective protein (target) can bind the active ingredient of a pharmaceutical composition and thereby changes its biological activity in response to the drug binding.

The term "tag" as used herein is meant to be understood in its broadest sense and to include, but is not limited to any suitable enzymatic, fluorescent, or radioactive labels and suitable epitopes, including but not limited to HA-tag, Myc-tag, T7, His-tag, FLAG-tag, Calmodulin binding proteins, glutathione-S-transferase, strep-tag, KT3-epitope, EEF-epitopes, green-fluorescent protein and variants thereof.

The term "therapeutics" as used herein, includes, but is not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments); antibodies thereto; nucleic acids encoding the component protein, and analogs or derivatives thereof; component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The term "vector" as used herein means a nucleic acid molecule capable of transporting another nucleic acid sequence to which it has been linked. Preferred vectors are those capable of autonomous replication and/or expression of nucleic acids to which they linked. The terms "plasmid" and "vector" are used interchangeably herein when applicable to the embodiment. However, vectors other than plasmids are also included herein. The expression elements of vectors vary in their strengths and specificities.

Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

#### 4. DETAILED DESCRIPTION OF THE INVENTION

##### Overview:

An object of the present invention was to identify protein complexes of the beta-amyloid precursor protein (APP) processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the protein complexes of the APP processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said protein complex were identified. The components are listed in table 1.

Said object is further achieved by the characterisation of component proteins. These proteins are listed in table 2.

The invention thus relates to the following embodiments:

4. A protein complex selected from complex (I) and comprising
  - (a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and
  - (b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions;
- and a complex (II) comprising at least two of said second proteins,

wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

5. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
6. A protein complex comprising the proteins selected from the proteins in table 1, third column or a homologue thereof, or a variant thereof or functionally active fragments or functionally active derivatives of said proteins, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions;  
wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC; 25 mM

Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, but 1 to the number of proteins listed in table 1, fifth column of said complex, or a homologue or a variant thereof, or a functionally active fragment or functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins of said fifth column under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.
5. The complex of any of No. 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

30. The complex of any of No. 1 - 7 that is involved in the biochemical activity as stated in table 3.
31. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps:  
Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
32. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
33. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
34. Component of a protein complex obtainable by a process according to any of No. 9 - 11.
35. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to No.1 (a) and at least one of said proteins, being selected from the second group of proteins according to No.1 (b).
36. Host cell, containing a vector comprising a construct of No. 13 or containing several vectors each comprising at least the nucleic acid encoding at least one protein selected from the first group of proteins according to No.1 (a) and the nucleic acid encoding at least one protein selected from the second group of proteins according to No.1 (b).

37. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
38. A kit comprising in one or more containers the complex of any of No. 1 - 8, optionally together with an antibody according to No. 17 and/or further components such as reagents and working instructions.
39. The kit according to No. 16 for processing a substrate of a complex of any one of No. 1 - 8.
40. The kit according to No. 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
41. Array in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 17 is attached to a solid carrier.
42. A process for processing a substrate of a complex of any one of No. 1 - 8 comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
43. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8.
44. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders, preferentially for diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
45. A method for screening for a molecule that binds to the complex of any one of No. 1 - 8, comprising the following steps:
  - (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.

46. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:
  - (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.
47. The method of No. 24, wherein the amount of said complex is determined.
48. The method of No. 25, wherein the activity of said complex is determined.
49. The method of No. 25, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
50. The method of No. 24, wherein the amount of the individual protein components of said complex are determined.

51. The method of No. 25, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.
30. The method of any of No. 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
34. A method for the production of a pharmaceutical composition comprising carrying out the method of No. 24 - 29 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
35. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous

sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.

34. The method of No. 33, wherein the amount of said complex is determined.
35. The method of No. 33, wherein the activity of said complex is determined.
36. The method of No. 35, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
37. The method of No. 33, wherein the amount of the individual protein components of said complex are determined.
38. The complex of any one of No. 1 - 8 or the antibody of fragment of No. 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.
40. The method according to No. 39, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
42. Complex of No. 1 - 8 and/or any of the proteins listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

Animal models are also provided herein.

Preferably, the protein components of the complexes described herein are all mammalian proteins. The complexes can also consist only of the respective homologues from other mammals such as mouse, rat, pig, cow, dog, monkey, sheep or horse or other species such as *D. melanogaster*, *C. elegans* or chicken. In another preferred embodiment, the complexes are a mixture of proteins from two or more species.

**TABLES:**

Table 1: Composition of Complexes

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Entry point'): Lists the bait proteins that have been chosen for the purification of the given complex.

Third column ('All interactors'): Lists all novel interactors which have been identified as members of the complex and all interactors which have been known to be associated with the bait so far.

Fourth column ('Known interactors'): Lists all interactors which have been known to be associated with the bait so far.

Fifth column ('Novel interactors of the complex'): Lists all novel interactors of the complex which have been identified in the experiments provided herein.

Table 2: Individual Proteins of the Complexes

First column ('Protein'): Lists in alphabetical order all proteins which have been identified as interactors of the complexes presented herein.

Second column ('SEQ ID'): Lists the SEQ ID (Sequence Identifications) of the proteins herein as used herein.

Third column ('IPI-Numbers'): Lists the IPI-Numbers of the proteins herein. The IPI-Numbers refer to the International Protein Index created by the European Bioinformatics Institute (EMBL-EBI), Hinxton, UK.

Fourth column ('Molecular Weight'): Lists the Molecular Weight of the proteins in Dalton.

**Table 3: Biochemical Activities of the Complexes of the invention.**

First column ('Name of complex'): Lists the name of the protein complexes as used herein.

Second column ('Biochemical Activity'): Lists biochemical activities of the complexes. Assays in order to test these activities are also provided herein (*infra*).

#### **4.1 PROTEIN COMPLEXES/PROTEINS OF THE INVENTION**

The protein complexes of the present invention and their component proteins are described in the Tables 1 - 3. The protein complexes and component proteins can be obtained by methods well known in the art for protein purification and recombinant protein expression. For example, the protein complexes of the present invention can be isolated using the TAP method described in Section 5, *infra*, and in WO 00/09716 and Rigaut et al., 1999, Nature Biotechnol. 17:1030-1032, which are each incorporated by reference in their entirety. Additionally, the protein complexes can be isolated by immunoprecipitation of the component proteins and combining the immunoprecipitated proteins. The protein complexes can also be produced by recombinantly expressing the component proteins and combining the expressed proteins.

The nucleic and amino acid sequences of the component proteins of the protein complexes of the present invention are provided herein (SEQ ID NO 1 - 152), and can be obtained by any method known in the art, e.g., by PCR amplification using synthetic primers hybridizable to the 3' and 5' ends of each sequence, and/or by cloning from a cDNA or genomic library using an oligonucleotide specific for each nucleotide sequence.

Homologues (e.g., nucleic acids encoding component proteins from other species) or other related sequences (e.g., variants, paralogs) which are members of a

native cellular protein complex can be obtained by low, moderate or high stringency hybridization with all or a portion of the particular nucleic acid sequence as a probe, using methods well known in the art for nucleic acid hybridization and cloning.

Exemplary moderately stringent hybridization conditions are as follows: prehybridization of filters containing DNA is carried out for 8 hours to overnight at 65°C in buffer composed of 6X SSC, 50 mM Tris-HCl (pH 7.5), 1 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.02% BSA, and 500 µg/ml denatured salmon sperm DNA. Filters are hybridized for 48 hours at 65°C in prehybridization mixture containing 100 µg/ml denatured salmon sperm DNA and 5-20 X 10<sup>6</sup> cpm of <sup>32</sup>P-labeled probe. Washing of filters is done at 37°C for 1 hour in a solution containing 2X SSC, 0.01% PVP, 0.01% Ficoll, and 0.01% BSA. This is followed by a wash in 0.1X SSC at 50 °C for 45 min before autoradiography. Alternatively, exemplary conditions of high stringency are as follows: e.g., hybridization to filter-bound DNA in 0.5 M NaHPO<sub>4</sub>, 7% sodium dodecyl sulfate (SDS), 1 mM EDTA at 65°C, and washing in 0.1xSSC/0.1% SDS at 68°C (Ausubel et al., eds., 1989, Current Protocols in Molecular Biology, Vol. I, Green Publishing Associates, Inc., and John Wiley & sons, Inc., New York, at p. 2.10.3). Other conditions of high stringency which may be used are well known in the art. Exemplary low stringency hybridization conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 µg/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

For recombinant expression of one or more of the proteins, the nucleic acid containing all or a portion of the nucleotide sequence encoding the protein can be inserted into an appropriate expression vector, i.e., a vector that contains the necessary elements for the transcription and translation of the inserted protein coding sequence. The necessary transcriptional and translational signals can also be supplied by the native promoter of the component protein gene, and/or flanking regions.

A variety of host-vector systems may be utilized to express the protein coding sequence. These include but are not limited to mammalian cell systems infected with virus (e.g., vaccinia virus, adenovirus, etc.); insect cell systems infected with virus (e.g., baculovirus); microorganisms such as yeast containing yeast vectors; or bacteria transformed with bacteriophage, DNA, plasmid DNA, or cosmid DNA. The expression

elements of vectors vary in their strengths and specificities. Depending on the host-vector system utilized, any one of a number of suitable transcription and translation elements may be used.

In a preferred embodiment, a complex of the present invention is obtained by expressing the entire coding sequences of the component proteins in the same cell, either under the control of the same promoter or separate promoters. In yet another embodiment, a derivative, fragment or homologue of a component protein is recombinantly expressed. Preferably the derivative, fragment or homologue of the protein forms a complex with the other components of the complex, and more preferably forms a complex that binds to an anti-complex antibody. Such an antibody is further described infra.

Any method available in the art can be used for the insertion of DNA fragments into a vector to construct expression vectors containing a chimeric gene consisting of appropriate transcriptional/translational control signals and protein coding sequences. These methods may include in vitro recombinant DNA and synthetic techniques and in vivo recombinant techniques (genetic recombination). Expression of nucleic acid sequences encoding a component protein, or a derivative, fragment or homologue thereof, may be regulated by a second nucleic acid sequence so that the gene or fragment thereof is expressed in a host transformed with the recombinant DNA molecule(s). For example, expression of the proteins may be controlled by any promoter/enhancer known in the art. In a specific embodiment, the promoter is not native to the gene for the component protein. Promoters that may be used can be selected from among the many known in the art, and are chosen so as to be operative in the selected host cell.

In a specific embodiment, a vector is used that comprises a promoter operably linked to nucleic acid sequences encoding a component protein, or a fragment, derivative or homologue thereof, one or more origins of replication, and optionally, one or more selectable markers (e.g., an antibiotic resistance gene).

In another specific embodiment, an expression vector containing the coding sequence, or a portion thereof, of a component protein, either together or separately, is made by subcloning the gene sequences into the EcoRI restriction site of each of the three pGEX vectors (glutathione S-transferase expression vectors; Smith and Johnson, 1988, Gene 7:31-40). This allows for the expression of products in the correct reading frame.

Expression vectors containing the sequences of interest can be identified by three general approaches: (a) nucleic acid hybridization, (b) presence or absence of "marker" gene function, and (c) expression of the inserted sequences. In the first approach, coding sequences can be detected by nucleic acid hybridization to probes comprising sequences homologous and complementary to the inserted sequences. In the second approach, the recombinant vector/host system can be identified and selected based upon the presence or absence of certain "marker" functions (e.g., resistance to antibiotics, occlusion body formation in baculovirus, etc.) caused by insertion of the sequences of interest in the vector. For example, if a component protein gene, or portion thereof, is inserted within the marker gene sequence of the vector, recombinants containing the encoded protein or portion will be identified by the absence of the marker gene function (e.g., loss of  $\beta$ -galactosidase activity). In the third approach, recombinant expression vectors can be identified by assaying for the component protein expressed by the recombinant vector. Such assays can be based, for example, on the physical or functional properties of the interacting species in in vitro assay systems, e.g., formation of a complex comprising the protein or binding to an anti-complex antibody.

Once recombinant component protein molecules are identified and the complexes or individual proteins isolated, several methods known in the art can be used to propagate them. Using a suitable host system and growth conditions, recombinant expression vectors can be propagated and amplified in quantity. As previously described, the expression vectors or derivatives which can be used include, but are not limited to, human or animal viruses such as vaccinia virus or adenovirus; insect viruses such as baculovirus, yeast vectors; bacteriophage vectors such as lambda phage; and plasmid and cosmid vectors.

In addition, a host cell strain may be chosen that modulates the expression of the inserted sequences, or modifies or processes the expressed proteins in the specific fashion desired. Expression from certain promoters can be elevated in the presence of certain inducers; thus expression of the genetically-engineered component proteins may be controlled. Furthermore, different host cells have characteristic and specific mechanisms for the translational and post-translational processing and modification (e.g., glycosylation, phosphorylation, etc.) of proteins. Appropriate cell lines or host systems can be chosen to ensure that the desired modification and processing of the foreign protein is achieved. For example, expression in a bacterial system can be used to produce an unglycosylated core protein, while expression in mammalian cells ensures

"native" glycosylation of a heterologous protein. Furthermore, different vector/host expression systems may effect processing reactions to different extents.

In other specific embodiments, a component protein or a fragment, homologue or derivative thereof, may be expressed as fusion or chimeric protein product comprising the protein, fragment, homologue, or derivative joined via a peptide bond to a heterologous protein sequence of a different protein. Such chimeric products can be made by ligating the appropriate nucleic acid sequences encoding the desired amino acids to each other by methods known in the art, in the proper coding frame, and expressing the chimeric products in a suitable host by methods commonly known in the art. Alternatively, such a chimeric product can be made by protein synthetic techniques, e.g., by use of a peptide synthesizer. Chimeric genes comprising a portion of a component protein fused to any heterologous protein-encoding sequences may be constructed.

In particular, protein component derivatives can be made by altering their sequences by substitutions, additions or deletions that provide for functionally equivalent molecules. Due to the degeneracy of nucleotide coding sequences, other DNA sequences that encode substantially the same amino acid sequence as a component gene or cDNA can be used in the practice of the present invention. These include but are not limited to nucleotide sequences comprising all or portions of the component protein gene that are altered by the substitution of different codons that encode a functionally equivalent amino acid residue within the sequence, thus producing a silent change. Likewise, the derivatives of the invention include, but are not limited to, those containing, as a primary amino acid sequence, all or part of the amino acid sequence of a component protein, including altered sequences in which functionally equivalent amino acid residues are substituted for residues within the sequence resulting in a silent change. For example, one or more amino acid residues within the sequence can be substituted by another amino acid of a similar polarity that acts as a functional equivalent, resulting in a silent alteration. Substitutes for an amino acid within the sequence may be selected from other members of the class to which the amino acid belongs. For example, the nonpolar (hydrophobic) amino acids include alanine, leucine, isoleucine, valine, proline, phenylalanine, tryptophan and methionine. The polar neutral amino acids include glycine, serine, threonine, cysteine, tyrosine, asparagine, and glutamine. The positively charged (basic) amino acids include arginine, lysine and

histidine. The negatively charged (acidic) amino acids include aspartic acid and glutamic acid.

In a specific embodiment, up to 1%, 2%, 5%, 10%, 15% or 20% of the total number of amino acids in the wild type protein are substituted or deleted; or 1, 2, 3, 4, 5, or 6 or up to 10 or up to 20 amino acids are inserted, substituted or deleted relative to the wild type protein.

In a specific embodiment of the invention, the nucleic acids encoding a protein component and protein components consisting of or comprising a fragment of or consisting of at least 6 (continuous) amino acids of the protein are provided. In other embodiments, the fragment consists of at least 10, 20, 30, 40, or 50 amino acids of the component protein. In specific embodiments, such fragments are not larger than 35, 100 or 200 amino acids. Derivatives or analogs of component proteins include, but are not limited, to molecules comprising regions that are substantially homologous to the component proteins, in various embodiments, by at least 30%, 40%, 50%, 60%, 70%, 80%, 90%, 95% or 99% identity over an amino acid sequence of identical size or when compared to an aligned sequence in which the alignment is done by a computer homology program known in the art, or whose encoding nucleic acid is capable of hybridizing to a sequence encoding the component protein under stringent, moderately stringent, or nonstringent conditions.

In a specific embodiment, proteins are provided herein, which share an identical region of 20, 30, 40, 50 or 60 contiguous amino acids of the proteins listed in table 2.

The protein component derivatives and analogs of the invention can be produced by various methods known in the art. The manipulations which result in their production can occur at the gene or protein level. For example, the cloned gene sequences can be modified by any of numerous strategies known in the art (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, 2d Ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, New York). The sequences can be cleaved at appropriate sites with restriction endonuclease(s), followed by further enzymatic modification if desired, isolated, and ligated in vitro. In the production of the gene encoding a derivative, homologue or analog of a component protein, care should be taken to ensure that the modified gene retains the original translational reading frame, uninterrupted by translational stop signals, in the gene region where the desired activity is encoded.

Additionally, the encoding nucleic acid sequence can be mutated in vitro or in vivo, to create and/or destroy translation, initiation, and/or termination sequences, or to

create variations in coding regions and/or form new restriction endonuclease sites or destroy pre-existing ones, to facilitate further in vitro modification. Any technique for mutagenesis known in the art can be used, including but not limited to, chemical mutagenesis and in vitro site-directed mutagenesis (Hutchinson et al., 1978, J. Biol. Chem. 253:6551-6558), amplification with PCR primers containing a mutation, etc.

Once a recombinant cell expressing a component protein, or fragment or derivative thereof, is identified, the individual gene product or complex can be isolated and analyzed. This is achieved by assays based on the physical and/or functional properties of the protein or complex, including, but not limited to, radioactive labeling of the product followed by analysis by gel electrophoresis, immunoassay, cross-linking to marker-labeled product, etc.

The component proteins and complexes may be isolated and purified by standard methods known in the art (either from natural sources or recombinant host cells expressing the complexes or proteins), including but not restricted to column chromatography (e.g., ion exchange, affinity, gel exclusion, reversed-phase high pressure, fast protein liquid, etc.), differential centrifugation, differential solubility, or by any other standard technique used for the purification of proteins. Functional properties may be evaluated using any suitable assay known in the art.

Alternatively, once a component protein or its derivative, is identified, the amino acid sequence of the protein can be deduced from the nucleic acid sequence of the chimeric gene from which it was encoded. As a result, the protein or its derivative can be synthesized by standard chemical methods known in the art (e.g., Hunkapiller et al., 1984, Nature 310:105-111).

Manipulations of component protein sequences may be made at the protein level. Included within the scope of the invention is a complex in which the component proteins or derivatives and analogs that are differentially modified during or after translation, e.g., by glycosylation, acetylation, phosphorylation, amidation, derivatization by known protecting/blocking groups, proteolytic cleavage, linkage to an antibody molecule or other cellular ligand, etc. Any of numerous chemical modifications may be carried out by known techniques, including but not limited to specific chemical cleavage by cyanogen bromide, trypsin, chymotrypsin, papain, V8 protease, NaBH<sub>4</sub>, acetylation, formylation, oxidation, reduction, metabolic synthesis in the presence of tunicamycin, etc.

In specific embodiments, the amino acid sequences are modified to include a fluorescent label. In another specific embodiment, the protein sequences are modified to

have a heterofunctional reagent; such heterofunctional reagents can be used to crosslink the members of the complex.

In addition, complexes of analogs and derivatives of component proteins can be chemically synthesized. For example, a peptide corresponding to a portion of a component protein, which comprises the desired domain or mediates the desired activity *in vitro* (e.g., complex formation) can be synthesized by use of a peptide synthesizer. Furthermore, if desired, non-classical amino acids or chemical amino acid analogs can be introduced as a substitution or addition into the protein sequence.

In cases where natural products are suspected of being mutant or are isolated from new species, the amino acid sequence of a component protein isolated from the natural source, as well as those expressed *in vitro*, or from synthesized expression vectors *in vivo* or *in vitro*, can be determined from analysis of the DNA sequence, or alternatively, by direct sequencing of the isolated protein. Such analysis can be performed by manual sequencing or through use of an automated amino acid sequenator.

The complexes can also be analyzed by hydrophilicity analysis (Hopp and Woods, 1981, Proc. Natl. Acad. Sci. USA 78:3824-3828). A hydrophilicity profile can be used to identify the hydrophobic and hydrophilic regions of the proteins, and help predict their orientation in designing substrates for experimental manipulation, such as in binding experiments, antibody synthesis, etc. Secondary structural analysis can also be done to identify regions of the component proteins, or their derivatives, that assume specific structures (Chou and Fasman, 1974, Biochemistry 13:222-23). Manipulation, translation, secondary structure prediction, hydrophilicity and hydrophobicity profile predictions, open reading frame prediction and plotting, and determination of sequence homologies, etc., can be accomplished using computer software programs available in the art.

Other methods of structural analysis including but not limited to X-ray crystallography (Engstrom, 1974, Biochem. Exp. Biol. 11:7-13), mass spectroscopy and gas chromatography (Methods in Protein Science, J. Wiley and Sons, New York, 1997), and computer modeling (Fletterick and Zoller, eds., 1986, Computer Graphics and Molecular Modeling, In: Current Communications in Molecular Biology, Cold Spring Harbor Laboratory, Cold Spring Harbor Press, New York) can also be employed.

#### 4.2 ANTIBODIES TO PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

According to the present invention, a protein complex of the present invention comprising a first protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fourth column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, selected from the group consisting of proteins listed in fifth column of table 1, or a functionally active fragment or functionally active derivative thereof, can be used as an immunogen to generate antibodies which immunospecifically bind such immunogen. According to the present invention, also a protein complex of the present invention can be used as an immunogen to generate antibodies which immunospecifically bind to such immunogen comprising all proteins listed in fifth column of table 1.

Such antibodies include, but are not limited to, polyclonal, monoclonal, chimeric, single chain, Fab fragments, and an Fab expression library. In a specific embodiment, antibodies to a complex comprising human protein components are produced. In another embodiment, a complex formed from a fragment of said first protein and a fragment of said second protein, which fragments contain the protein domain that interacts with the other member of the complex, are used as an immunogen for antibody production. In a preferred embodiment, the antibody specific for the complex in that the antibody does not bind the individual protein components of the complex.

Polyclonal antibodies can be prepared as described above by immunizing a suitable subject with a polypeptide of the invention as an immunogen. Preferred polyclonal antibody compositions are ones that have been selected for antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred polyclonal antibody preparations are ones that contain only antibodies directed against a polypeptide or polypeptides of the invention. Particularly preferred immunogen compositions are those that contain no other human proteins such as, for example, immunogen compositions made using a non-human host cell for recombinant expression of a polypeptide of the invention. In such a manner, the only human epitope or epitopes recognized by the resulting antibody compositions raised against this immunogen will be present as part of a polypeptide or polypeptides of the invention.

The antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA)

using immobilized polypeptide. If desired, the antibody molecules can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. Alternatively, antibodies specific for a protein or polypeptide of the invention can be selected for (e.g., partially purified) or purified by, e.g., affinity chromatography. For example, a recombinantly expressed and purified (or partially purified) protein of the invention is produced as described herein, and covalently or non-covalently coupled to a solid support such as, for example, a chromatography column. The column can then be used to affinity purify antibodies specific for the proteins of the invention from a sample containing antibodies directed against a large number of different epitopes, thereby generating a substantially purified antibody composition, i.e., one that is substantially free of contaminating antibodies. By a substantially purified antibody composition is meant, in this context, that the antibody sample contains at most only 30% (by dry weight) of contaminating antibodies directed against epitopes other than those on the desired protein or polypeptide of the invention, and preferably at most 20%, yet more preferably at most 10%, and most preferably at most 5% (by dry weight) of the sample is contaminating antibodies. A purified antibody composition means that at least 99% of the antibodies in the composition are directed against the desired protein or polypeptide of the invention.

At an appropriate time after immunization, e.g., when the specific antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein, 1975, *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al., 1983, *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al., 1985, *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (see generally *Current Protocols in Immunology* 1994, Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind the polypeptide of interest, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal antibody directed against a polypeptide of the invention can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with the polypeptide of interest. Kits for generating and screening phage

display libraries are commercially available (e.g., the Pharmacia Recombinant Phage Antibody System, Catalog No. 27-9400-01; and the Stratagene SurfZAP Phage Display Kit, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al., 1991, *Bio/Technology* 9:1370-1372; Hay et al., 1992, *Hum. Antibod. Hybridomas* 3:81-85; Huse et al., 1989, *Science* 246:1275-1281; Griffiths et al., 1993, *EMBO J.* 12:725-734.

Additionally, recombinant antibodies, such as chimeric and humanized monoclonal antibodies, comprising both human and non-human portions, which can be made using standard recombinant DNA techniques, are within the scope of the invention. A chimeric antibody is a molecule in which different portions are derived from different animal species, such as those having a variable region derived from a murine mAb and a human immunoglobulin constant region. (See, e.g., Cabilly et al., U.S. Patent No. 4,816,567; and Boss et al., U.S. Patent No. 4,816,397, which are incorporated herein by reference in their entirety.) Humanized antibodies are antibody molecules from non-human species having one or more complementarily determining regions (CDRs) from the non-human species and a framework region from a human immunoglobulin molecule. (See, e.g., Queen, U.S. Patent No. 5,585,089, which is incorporated herein by reference in its entirety.) Such chimeric and humanized monoclonal antibodies can be produced by recombinant DNA techniques known in the art, for example using methods described in PCT Publication No. WO 87/02671; European Patent Application 184,187; European Patent Application 171,496; European Patent Application 173,494; PCT Publication No. WO 86/01533; U.S. Patent No. 4,816,567; European Patent Application 125,023; Better et al., 1988, *Science* 240:1041-1043; Liu et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:3439-3443; Liu et al., 1987, *J. Immunol.* 139:3521-3526; Sun et al., 1987, *Proc. Natl. Acad. Sci. USA* 84:214-218; Nishimura et al., 1987, *Canc. Res.* 47:999-1005; Wood et al., 1985, *Nature* 314:446-449; and Shaw et al., 1988, *J. Natl. Cancer Inst.* 80:1553-1559); Morrison, 1985, *Science* 229:1202-1207; Oi et al., 1986, *Bio/Techniques* 4:214; U.S. Patent 5,225,539; Jones et al., 1986, *Nature* 321:552-525; Verhoeyan et al., 1988, *Science* 239:1534; and Beidler et al., 1988, *J. Immunol.* 141:4053-4060.

Completely human antibodies are particularly desirable for therapeutic treatment of human patients. Such antibodies can be produced, for example, using transgenic mice which are incapable of expressing endogenous immunoglobulin heavy and light chains genes, but which can express human heavy and light chain genes. The transgenic mice are immunized in the normal fashion with a selected antigen, e.g., all or a portion of a polypeptide of the invention. Monoclonal antibodies directed against the antigen can be obtained using conventional hybridoma technology. The human immunoglobulin transgenes harbored by the transgenic mice rearrange during B cell differentiation, and subsequently undergo class switching and somatic mutation. Thus, using such a technique, it is possible to produce therapeutically useful IgG, IgA and IgE antibodies. For an overview of this technology for producing human antibodies, see Lonberg and Huszar, 1995, *Int. Rev. Immunol.* 13:65-93). For a detailed discussion of this technology for producing human antibodies and human monoclonal antibodies and protocols for producing such antibodies, see, e.g., U.S. Patent 5,625,126; U.S. Patent 5,633,425; U.S. Patent 5,569,825; U.S. Patent 5,661,016; and U.S. Patent 5,545,806. In addition, companies such as Abgenix, Inc. (Freemont, CA), can be engaged to provide human antibodies directed against a selected antigen using technology similar to that described above.

Completely human antibodies which recognize a selected epitope can be generated using a technique referred to as "guided selection." In this approach a selected non-human monoclonal antibody, e.g., a murine antibody, is used to guide the selection of a completely human antibody recognizing the same epitope. (Jespers et al., 1994, *Bio/technology* 12:899-903).

Antibody fragments that contain the idiotypes of the complex can be generated by techniques known in the art. For example, such fragments include, but are not limited to, the F(ab')2 fragment which can be produced by pepsin digestion of the antibody molecule; the Fab' fragment that can be generated by reducing the disulfide bridges of the F(ab')2 fragment; the Fab fragment that can be generated by treating the antibody molecular with papain and a reducing agent; and Fv fragments.

In the production of antibodies, screening for the desired antibody can be accomplished by techniques known in the art, e.g., ELISA (enzyme-linked immunosorbent assay). To select antibodies specific to a particular domain of the complex, or a derivative thereof, one may assay generated hybridomas for a product that binds to the fragment of the complex, or a derivative thereof, that contains such a

domain. For selection of an antibody that specifically binds a complex of the present, or a derivative, or homologue thereof, but which does not specifically bind to the individual proteins of the complex, or a derivative, or homologue thereof, one can select on the basis of positive binding to the complex and a lack of binding to the individual protein components.

Antibodies specific to a domain of the complex, or a derivative, or homologue thereof, are also provided.

The foregoing antibodies can be used in methods known in the art relating to the localization and/or quantification of the complexes of the invention, e.g., for imaging these proteins, measuring levels thereof in appropriate physiological samples (by immunoassay), in diagnostic methods, etc. This hold true also for a derivative, or homologue thereof of a complex.

In another embodiment of the invention (see *infra*), an antibody to a complex or a fragment of such antibodies containing the antibody binding domain, is a therapeutic.

#### 4.3 DIAGNOSTIC, PROGNOSTIC, AND SCREENING USES OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The particular protein complexes and proteins of the present invention may be markers of normal physiological processes, and thus have diagnostic utility. Further, definition of particular groups of patients with elevations or deficiencies of a protein complex of the present invention, or wherein the protein complex has a change in protein component composition, can lead to new nosological classifications of diseases, furthering diagnostic ability.

Detecting levels of protein complexes, or individual component proteins that form the complexes, or detecting levels of the mRNAs encoding the components of the complex, may be used in diagnosis, prognosis, and/or staging to follow the course of a disease state, to follow a therapeutic response, etc.

A protein complex of the present invention and the individual components of the complex and a derivative, analog or subsequence thereof, encoding nucleic acids (and sequences complementary thereto), and anti-complex antibodies and antibodies directed against individual components that can form the complex, are useful in diagnostics. The foregoing molecules can be used in assays, such as immunoassays, to detect,

prognose, diagnose, or monitor various conditions, diseases, and disorders characterized by aberrant levels of a complex or aberrant component composition of a complex, or monitor the treatment of such various conditions, diseases, and disorders.

In particular, such an immunoassay is carried out by a method comprising contacting a sample derived from a patient with an anti-complex antibody under conditions such that immunospecific binding can occur, and detecting or measuring the amount of any immunospecific binding by the antibody. In a specific aspect, such binding of antibody, in tissue sections, can be used to detect aberrant complex localization, or aberrant (e.g., high, low or absent) levels of a protein complex or complexes. In a specific embodiment, an antibody to the complex can be used to assay a patient tissue or serum sample for the presence of the complex, where an aberrant level of the complex is an indication of a diseased condition. By "aberrant levels" is meant increased or decreased levels relative to that present, or a standard level representing that present, in an analogous sample from a portion or fluid of the body, or from a subject not having the disorder.

The immunoassays which can be used include but are not limited to competitive and non-competitive assay systems using techniques such as Western blots, radioimmunoassays, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoprecipitation assays, precipitin reactions, gel diffusion precipitin reactions, immunodiffusion assays, agglutination assays, complement-fixation assays, immunoradiometric assays, fluorescent immunoassays, protein A immunoassays, to name but a few known in the art.

Nucleic acids encoding the components of the protein complex and related nucleic acid sequences and subsequences, including complementary sequences, can be used in hybridization assays. The nucleic acid sequences, or subsequences thereof, comprising about at least 8 nucleotides, can be used as hybridization probes. Hybridization assays can be used to detect, prognose, diagnose, or monitor conditions, disorders, or disease states associated with aberrant levels of the mRNAs encoding the components of a complex as described, supra. In particular, such a hybridization assay is carried out by a method comprising contacting a sample containing nucleic acid with a nucleic acid probe capable of hybridizing to component protein coding DNA or RNA, under conditions such that hybridization can occur, and detecting or measuring any resulting hybridization.

In specific embodiments, diseases and disorders involving or characterized by aberrant levels of a protein complex or aberrant complex composition can be diagnosed, or its suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by determining the component protein composition of the complex, or detecting aberrant levels of a member of the complex or un-complexed component proteins or encoding nucleic acids, or functional activity including, but not restricted to, binding to an interacting partner, or by detecting mutations in component protein RNA, DNA or protein (e.g., mutations such as translocations, truncations, changes in nucleotide or amino acid sequence relative to wild-type that cause increased or decreased expression or activity of a complex, and/or component protein.

By way of example, levels of a protein complex and the individual components of a complex can be detected by immunoassay, levels of component protein RNA or DNA can be detected by hybridization assays (e.g., Northern blots, dot blots, RNase protection assays), and binding of component proteins to each other (e.g., complex formation) can be measured by binding assays commonly known in the art. Translocations and point mutations in component protein genes can be detected by Southern blotting, RFLP analysis, PCR using primers that preferably generate a fragment spanning at least most of the gene by sequencing of genomic DNA or cDNA obtained from the patient, etc.

Assays well known in the art (e.g., assays described above such as immunoassays, nucleic acid hybridization assays, activity assays, etc.) can be used to determine whether one or more particular protein complexes are present at either increased or decreased levels, or are absent, in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the levels in samples from subjects not having such a disease or disorder, or having a predisposition to develop such a disease or disorder. Additionally, these assays can be used to determine whether the ratio of the complex to the un-complexed components of the complex, is increased or decreased in samples from patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, as compared to the ratio in samples from subjects not having such a disease or disorder.

In the event that levels of one or more particular protein complexes (i.e., complexes formed from component protein derivatives, homologs, fragments, or analogs) are determined to be increased in patients suffering from a particular disease or

disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder, or predisposition for a disease or disorder, can be diagnosed, have prognosis defined for, be screened for, or be monitored by detecting increased levels of the one or more protein complexes, increased levels of the mRNA that encodes one or more members of the one or more particular protein complexes, or by detecting increased complex functional activity.

Accordingly, in a specific embodiment of the present invention, diseases and disorders involving increased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting increased levels of the one or more protein complexes, the mRNA encoding both members of the complex, or complex functional activity, or by detecting mutations in the component proteins that stabilize or enhance complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that stabilize or enhance complex formation.

In the event that levels of one or more particular protein complexes are determined to be decreased in patients suffering from a particular disease or disorder, or having a predisposition to develop such a disease or disorder, then the particular disease or disorder or predisposition for a disease or disorder can be diagnosed, have its prognosis determined, be screened for, or be monitored by detecting decreased levels of the one or more protein complexes, the mRNA that encodes one or more members of the particular one or more protein complexes, or by detecting decreased protein complex functional activity.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving decreased levels of one or more protein complexes can be diagnosed, or their suspected presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting decreased levels of the one or more protein complexes, the mRNA encoding one or more members of the one or more complexes, or complex functional activity, or by detecting mutations in the component proteins that decrease complex formation, e.g., mutations such as translocations in nucleic acids, truncations in the gene or protein, changes in nucleotide or amino acid sequence relative to wild-type, that decrease complex formation.

Accordingly, in a specific embodiment of the invention, diseases and disorders involving aberrant compositions of the complexes can be diagnosed, or their suspected

presence can be screened for, or a predisposition to develop such disorders can be detected, by detecting the component proteins of one or more complexes, or the mRNA encoding the members of the one or more complexes.

The use of detection techniques, especially those involving antibodies against a protein complex, provides a method of detecting specific cells that express the complex or component proteins. Using such assays, specific cell types can be defined in which one or more particular protein complexes are expressed, and the presence of the complex or component proteins can be correlated with cell viability, state, health, etc.

Also embodied are methods to detect a protein complex of the present invention in cell culture models that express particular protein complexes or derivatives thereof, for the purpose of characterizing or preparing the complexes for harvest. This embodiment includes cell sorting of prokaryotes such as but not restricted to bacteria (Davey and Kell, 1996, *Microbiol. Rev.* 60:641-696), primary cultures and tissue specimens from eukaryotes, including mammalian species such as human (Steele et al., 1996, *Clin. Obstet. Gynecol.* 39:801-813), and continuous cell cultures (Orfao and Ruiz-Arguelles, 1996, *Clin. Biochem.* 29:5-9). Such isolations can be used as methods of diagnosis, described, supra.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation.

Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus

have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

#### 4.4 THERAPEUTIC USES OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

The present invention is directed to a method for treatment or prevention of various diseases and disorders by administration of a therapeutic compound (termed herein "therapeutic"). Such "therapeutics" include, but are not limited to, a protein complex of the present invention, the individual component proteins, and analogs and derivatives (including fragments) of the foregoing (e.g., as described hereinabove); antibodies thereto (as described hereinabove); nucleic acids encoding the component protein, and analogs or derivatives, thereof (e.g., as described hereinabove); component protein antisense nucleic acids, and agents that modulate complex formation and/or activity (i.e., agonists and antagonists).

The protein complexes as identified herein can be implicated in processes which are implicated in or associated with pathological conditions.

These disorders are treated or prevented by administration of a therapeutic that modulates (i.e. inhibits or promotes) protein complex activity or formation or modulates its function or composition. Diseases or disorders associated with aberrant levels of complex activity or formation, or aberrant levels or activity of the component proteins, or aberrant complex composition or a change in the function, may be treated by administration of a therapeutic that modulates complex formation or activity or by the administration of a protein complex.

Therapeutics may also be administered to modulate complex formation or activity or level thereof in a microbial organism such as yeast, fungi such as candida albicans causing an infectious disease in animals or humans.

Diseases and disorders characterized by increased (relative to a subject not suffering from the disease or disorder) complex levels or activity can be treated with therapeutics that antagonize (i.e., reduce or inhibit) complex formation or activity. Therapeutics that can be used include, but are not limited to, the component proteins or an analog, derivative or fragment of the component protein; anti-complex antibodies (e.g., antibodies specific for the protein complex, or a fragment or derivative of the antibody containing the binding region thereof; nucleic acids encoding the component proteins; antisense nucleic acids complementary to nucleic acids encoding the component proteins; and nucleic acids encoding the component protein that are dysfunctional due to, e.g., a heterologous insertion within the protein coding sequence, that are used to "knockout" endogenous protein function by homologous recombination, see, e.g., Capecchi, 1989, Science 244:1288-1292. In one embodiment, a therapeutic is 1, 2 or more antisense nucleic acids which are complementary to 1, 2, or more nucleic acids, respectfully, that encode component proteins of a complex.

In a specific embodiment of the present invention, a nucleic acid containing a portion of a component protein gene in which gene sequences flank (are both 5' and 3' to) a different gene sequence, is used as a component protein antagonist, or to promote component protein inactivation by homologous recombination (see also, Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA 86:8932-8935; Zijlstra et al., 1989, Nature 342: 435-438). Additionally, mutants or derivatives of a component protein that has greater affinity for another component protein or the complex than wild type may be administered to compete with wild type protein for binding, thereby reducing the levels of complexes containing the wild type protein. Other therapeutics that inhibit complex function can be identified by use of known convenient in vitro assays, e.g., based on their ability to inhibit complex formation, or as described in Section 4.5, infra.

In specific embodiments, therapeutics that antagonize complex formation or activity are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an increased (relative to normal or desired) level of a complex, for example, in patients where complexes are overactive or overexpressed; or (2) in diseases or disorders where an in vitro (or in vivo) assay (see infra) indicates the utility of antagonist administration. Increased levels of a complex can be readily detected, e.g.,

by quantifying protein and/or RNA, by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, or structure and/or activity of the expressed complex (or the encoding mRNA). Many methods standard in the art can be thus employed including, but not limited to, immunoassays to detect complexes and/or visualize complexes (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.), and/or hybridization assays to detect concurrent expression of component protein mRNA (e.g., Northern assays, dot blot analysis, in situ hybridization, etc.).

A more specific embodiment of the present invention is directed to a method of reducing complex expression (i.e., expression of the protein components of the complex and/or formation of the complex) by targeting mRNAs that express the protein moieties. RNA therapeutics currently fall within three classes, antisense species, ribozymes, or RNA aptamers (Good et al., 1997, Gene Therapy 4:45-54).

Antisense oligonucleotides have been the most widely used. By way of example, but not limitation, antisense oligonucleotide methodology to reduce complex formation is presented below, infra. Ribozyme therapy involves the administration, induced expression, etc. of small RNA molecules with enzymatic ability to cleave, bind, or otherwise inactivate specific RNAs, to reduce or eliminate expression of particular proteins (Grassi and Marini, 1996, Annals of Medicine 28:499-510; Gibson, 1996, Cancer and Metastasis Reviews 15:287-299). RNA aptamers are specific RNA ligand proteins, such as for Tat and Rev RNA (Good et al., 1997, Gene Therapy 4:45-54) that can specifically inhibit their translation. Aptamers specific for component proteins can be identified by many methods well known in the art, for example, by affecting the formation of a complex in the protein-protein interaction assay described, infra.

In another embodiment, the activity or levels of a component protein are reduced by administration of another component protein, or the encoding nucleic acid, or an antibody that immunospecifically binds to the component protein, or a fragment or a derivative of the antibody containing the binding domain thereof.

In another aspect of the invention, diseases or disorders associated with increased levels of an component protein of the complex may be treated or prevented by administration of a therapeutic that increases complex formation if the complex formation acts to reduce or inactivate the component protein through complex formation. Such diseases or disorders can be treated or prevented by administration of one component

member of the complex, administration of antibodies or other molecules that stabilize the complex, etc.

Diseases and disorders associated with underexpression of a complex, or a component protein, are treated or prevented by administration of a therapeutic that promotes (i.e., increases or supplies) complex levels and/or function, or individual component protein function. Examples of such a therapeutic include but are not limited to a complex or a derivative, analog or fragment of the complex that are functionally active (e.g., able to form a complex), un-complexed component proteins and derivatives, analogs, and fragments of un-complexed component proteins, and nucleic acids encoding the members of a complex or functionally active derivatives or fragments of the members of the complex, e.g., for use in gene therapy. In a specific embodiment, a therapeutic includes derivatives, homologs or fragments of a component protein that increase and/or stabilize complex formation. Examples of other agonists can be identified using in vitro assays or animal models, examples of which are described, infra.

In yet other specific embodiments of the present invention, therapeutics that promote complex function are administered therapeutically, including prophylactically, (1) in diseases or disorders involving an absence or decreased (relative to normal or desired) level of a complex, for example, in patients where a complex, or the individual components necessary to form the complex, is lacking, genetically defective, biologically inactive or underactive, or under-expressed; or (2) in diseases or disorders wherein an in vitro or in vivo assay (see, infra) indicates the utility of complex agonist administration. The absence or decreased level of a complex, component protein or function can be readily detected, e.g., by obtaining a patient tissue sample (e.g., from biopsy tissue) and assaying it in vitro for RNA or protein levels, structure and/or activity of the expressed complex and/or the concurrent expression of mRNA encoding the two components of the complex. Many methods standard in the art can be thus employed, including but not limited to immunoassays to detect and/or visualize a complex, or the individual components of a complex (e.g., Western blot analysis, immunoprecipitation followed by sodium dodecyl sulfate polyacrylamide gel electrophoresis [SDS-PAGE], immunocytochemistry, etc.) and/or hybridization assays to detect expression of mRNAs encoding the individual protein components of a complex by detecting and/or visualizing component mRNA concurrently or separately using, e.g., Northern assays, dot blot analysis, in situ hybridization, etc.

In specific embodiments, the activity or levels of a component protein are increased by administration of another component protein of the same complex, or a derivative, homolog or analog thereof, a nucleic acid encoding the other component, or an agent that stabilizes or enhances the other component, or a fragment or derivative of such an agent.

Generally, administration of products of species origin or species reactivity (in the case of antibodies) that is the same species as that of the patient is preferred. Thus, in a preferred embodiment, a human complex, or derivative, homolog or analog thereof; nucleic acids encoding the members of the human complex or a derivative, homolog or analog thereof; an antibody to a human complex, or a derivative thereof; or other human agents that affect component proteins or the complex, are therapeutically or prophylactically administered to a human patient.

Preferably, suitable in vitro or in vivo assays are utilized to determine the effect of a specific therapeutic and whether its administration is indicated for treatment of the affected tissue or individual.

In various specific embodiments, in vitro assays can be carried out with representative cells of cell types involved in a patient's disorder, to determine if a therapeutic has a desired effect upon such cell types.

Compounds for use in therapy can be tested in suitable animal model systems prior to testing in humans, including, but not limited to, rats, mice, chicken, cows, monkeys, rabbits, etc. For in vivo testing, prior to administration to humans, any animal model system known in the art may be used. Additional descriptions and sources of therapeutics that can be used according to the invention are found in Sections 4.1 to 4.3 and 4.7 herein.

#### 4.4.1 GENE THERAPY

In a specific embodiment of the present invention, nucleic acids comprising a sequence encoding the component proteins, or a functional derivative thereof, are administered to modulate complex activity or formation by way of gene therapy. Gene therapy refers to therapy performed by the administration of a nucleic acid to a subject. In this embodiment of the present invention, the nucleic acid expresses its encoded protein(s) that mediates a therapeutic effect by modulating complex activity or formation.

Any of the methods for gene therapy available in the art can be used according to the present invention. Exemplary methods are described below.

For general reviews of the methods of gene therapy, see Goldspiel et al., 1993, Clinical Pharmacy 12:488-505; Wu and Wu, 1991, Biotherapy 3:87-95; Tolstoshev, 1993, Ann. Rev. Pharmacol. Toxicol. 32:573-596; Mulligan, 1993, Science 260:926-932; Morgan and Anderson, 1993, Ann. Rev. Biochem. 62:191-217; and May, 1993, TIBTECH 11:155-215. Methods commonly known in the art of recombinant DNA technology which can be used are described in Ausubel et al., eds., 1993, Current Protocols in Molecular Biology, John Wiley & Sons, NY; and Kriegler, 1990, Gene Transfer and Expression, A Laboratory Manual, Stockton Press, NY.

In a preferred aspect, the therapeutic comprises a nucleic acid that is part of an expression vector that expresses one or more of the component proteins, or fragments or chimeric proteins thereof, in a suitable host. In particular, such a nucleic acid has a promoter operably linked to the protein coding region(s) (or, less preferably separate promoters linked to the separate coding regions separately), said promoter being inducible or constitutive, and optionally, tissue-specific. In another particular embodiment, a nucleic acid molecule is used in which the coding sequences, and any other desired sequences, are flanked by regions that promote homologous recombination at a desired site in the genome, thus providing for intra-chromosomal expression of the component protein nucleic acids (Koller and Smithies, 1989, Proc. Natl. Acad. Sci. USA 86:8932-8935; Zijlstra et al., 1989, Nature 342:435-438).

Delivery of the nucleic acid into a patient may be either direct, in which case the patient is directly exposed to the nucleic acid or nucleic acid-carrying vector, or indirect, in which case, cells are first transformed with the nucleic acid *in vitro*, then transplanted into the patient. These two approaches are known, respectively, as *in vivo* or *ex vivo* gene therapy.

In a specific embodiment, the nucleic acid is directly administered *in vivo*, where it is expressed to produce the encoded product. This can be accomplished by any of numerous methods known in the art, e.g., by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by infection using a defective or attenuated retroviral or other viral vector (U.S. Patent No. 4,980,286), or by direct injection of naked DNA, or by use of microparticle bombardment (e.g., a gene gun; Biostatic, Dupont), or coating with lipids or cell-surface receptors, or through use of transfecting agents, by encapsulation in liposomes,

microparticles, or microcapsules, or by administering it in linkage to a peptide that is known to enter the nucleus, or by administering it in linkage to a ligand subject to receptor-mediated endocytosis that can be used to target cell types specifically expressing the receptors (e.g., Wu and Wu, 1987, *J. Biol. Chem.* 262:4429-4432), etc. In another embodiment, a nucleic acid-ligand complex can be formed in which the ligand comprises a fusogenic viral peptide that disrupts endosomes, allowing the nucleic acid to avoid lysosomal degradation. In yet another embodiment, the nucleic acid can be targeted *in vivo* for cell specific uptake and expression, by targeting a specific receptor (see, e.g., International Patent Publications WO 92/06180; WO 92/22635; WO 92/20316; WO 93/14188; and WO 93/20221. Alternatively, the nucleic acid can be introduced intracellularly and incorporated within host cell DNA for expression, by homologous recombination (Koller and Smithies, 1989, *Proc. Natl. Acad. Sci. USA* 86:8932-8935; Zijlstra et al., 1989, *Nature* 342:435-438).

In a specific embodiment, a viral vector that contains the component protein encoding nucleic acids is used. For example, a retroviral vector can be used (Miller et al., 1993, *Meth. Enzymol.* 217:581-599). These retroviral vectors have been modified to delete retroviral sequences that are not necessary for packaging of the viral genome and integration into host cell DNA. The encoding nucleic acids to be used in gene therapy is/are cloned into the vector, which facilitates delivery of the gene into a patient. More detail about retroviral vectors can be found in Boesen et al., 1994, *Biotherapy* 6:291-302, which describes the use of a retroviral vector to deliver the mdr1 gene to hematopoietic stem cells in order to make the stem cells more resistant to chemotherapy. Other references illustrating the use of retroviral vectors in gene therapy are Clowes et al., 1994, *J. Clin. Invest.* 93:644-651; Kiem et al., 1994, *Blood* 83:1467-1473; Salmons and Gunzberg, 1993, *Human Gene Therapy* 4:129-141; and Grossman and Wilson, 1993, *Curr. Opin. in Genetics and Devel.* 3:110-114.

Adenoviruses are other viral vectors that can be used in gene therapy. Adenoviruses are especially attractive vehicles for delivering genes to respiratory epithelia. Adenoviruses naturally infect respiratory epithelia where they cause a mild disease. Other targets for adenovirus-based delivery systems are the liver, the central nervous system, endothelial cells and muscle. Adenoviruses have the advantage of being capable of infecting non-dividing cells. Kozarsky and Wilson, 1993, *Curr. Opin. Genet. Devel.* 3:499-503, discuss adenovirus-based gene therapy. The use of adenovirus vectors to transfer genes to the respiratory epithelia of rhesus monkeys has

been demonstrated by Bout et al., 1994, Human Gene Therapy 5:3-10. Other instances of the use of adenoviruses in gene therapy can be found in Rosenfeld et al., 1991, Science 252:431-434; Rosenfeld et al., 1992, Cell 68:143-155; and Mastrangeli et al., 1993, J. Clin. Invest. 91:225-234.

Adeno-associated virus (AAV) has also been proposed for use in gene therapy (Walsh et al., 1993, Proc. Soc. Exp. Biol. Med. 204:289-300.

Another approach to gene therapy involves transferring a gene into cells in tissue culture by methods such as electroporation, lipofection, calcium phosphate-mediated transfection, or viral infection. Usually, the method of transfer includes the transfer of a selectable marker to the cells. The cells are then placed under selection to isolate those cells that have taken up and are expressing the transferred gene from those that have not. Those cells are then delivered to a patient.

In this embodiment, the nucleic acid is introduced into a cell prior to administration *in vivo* of the resulting recombinant cell. Such introduction can be carried out by any method known in the art including, but not limited to, transfection by electroporation, microinjection, infection with a viral or bacteriophage vector containing the nucleic acid sequences, cell fusion, chromosome-mediated gene transfer, microcell-mediated gene transfer, spheroplast fusion, etc. Numerous techniques are known in the art for the introduction of foreign genes into cells (see, e.g., Loeffler and Behr, 1993, Meth. Enzymol. 217:599-618; Cohen et al., 1993, Meth. Enzymol. 217:618-644; Cline, 1985, Pharmac. Ther. 29:69-92) and may be used in accordance with the present invention, provided that the necessary developmental and physiological functions of the recipient cells are not disrupted. The technique should provide for the stable transfer of the nucleic acid to the cell, so that the nucleic acid is expressible by the cell and preferably, is heritable and expressible by its cell progeny.

The resulting recombinant cells can be delivered to a patient by various methods known in the art. In a preferred embodiment, epithelial cells are injected, e.g., subcutaneously. In another embodiment, recombinant skin cells may be applied as a skin graft onto the patient. Recombinant blood cells (e.g., hematopoietic stem or progenitor cells) are preferably administered intravenously. The amount of cells envisioned for use depends on the desired effect, patient state, etc., and can be determined by one skilled in the art.

Cells into which a nucleic acid can be introduced for purposes of gene therapy encompass any desired, available cell type, and include but are not limited to epithelial

cells, endothelial cells, keratinocytes, fibroblasts, muscle cells, hepatocytes, blood cells such as T lymphocytes, B lymphocytes, monocytes, macrophages, neutrophils, eosinophils, megakaryocytes, and granulocytes, various stem or progenitor cells, in particular hematopoietic stem or progenitor cells, e.g., as obtained from bone marrow, umbilical cord blood, peripheral blood, fetal liver, etc.

In a preferred embodiment, the cell used for gene therapy is autologous to the patient.

In an embodiment in which recombinant cells are used in gene therapy, a component protein encoding nucleic acid is/are introduced into the cells such that the gene or genes are expressible by the cells or their progeny, and the recombinant cells are then administered *in vivo* for therapeutic effect. In a specific embodiment, stem or progenitor cells are used. Any stem and/or progenitor cells which can be isolated and maintained *in vitro* can potentially be used in accordance with this embodiment of the present invention. Such stem cells include but are not limited to hematopoietic stem cells (HSCs), stem cells of epithelial tissues such as the skin and the lining of the gut, embryonic heart muscle cells, liver stem cells (International Patent Publication WO 94/08598), and neural stem cells (Stemple and Anderson, 1992, Cell 71:973-985).

Epithelial stem cells (ESCs), or keratinocytes, can be obtained from tissues such as the skin and the lining of the gut by known procedures (Rheinwald, 1980, Meth. Cell Biol. 2A:229). In stratified epithelial tissue such as the skin, renewal occurs by mitosis of stem cells within the germinal layer, the layer closest to the basal lamina. Similarly, stem cells within the lining of the gut provide for a rapid renewal rate of this tissue. ESCs or keratinocytes obtained from the skin or lining of the gut of a patient or donor can be grown in tissue culture (Rheinwald, 1980, Meth. Cell Bio. 2A:229; Pittelkow and Scott, 1986, Mayo Clinic Proc. 61:771). If the ESCs are provided by a donor, a method for suppression of host versus graft reactivity (e.g., irradiation, or drug or antibody administration to promote moderate immunosuppression) can also be used.

With respect to hematopoietic stem cells (HSCs), any technique that provides for the isolation, propagation, and maintenance *in vitro* of HSCs can be used in this embodiment of the invention. Techniques by which this may be accomplished include (a) the isolation and establishment of HSC cultures from bone marrow cells isolated from the future host, or a donor, or (b) the use of previously established long-term HSC cultures, which may be allogeneic or xenogeneic. Non-autologous HSCs are used preferably in conjunction with a method of suppressing transplantation immune reactions

between the future host and patient. In a particular embodiment of the present invention, human bone marrow cells can be obtained from the posterior iliac crest by needle aspiration (see, e.g., Kodo et al., 1984, J. Clin. Invest. 73: 1377-1384). In a preferred embodiment of the present invention, the HSCs can be made highly enriched or in substantially pure form. This enrichment can be accomplished before, during, or after long-term culturing, and can be done by any technique known in the art. Long-term cultures of bone marrow cells can be established and maintained by using, for example, modified Dexter cell culture techniques (Dexter et al., 1977, J. Cell Physiol. 91:335) or Witlock-Witte culture techniques (Witlock and Witte, 1982, Proc. Natl. Acad. Sci. USA 79:3608-3612).

In a specific embodiment, the nucleic acid to be introduced for purposes of gene therapy comprises an inducible promoter operably linked to the coding region, such that expression of the nucleic acid is controllable by controlling the presence or absence of the appropriate inducer of transcription.

Additional methods can be adapted for use to deliver a nucleic acid encoding the component proteins, or functional derivatives thereof, e.g., as described in Section 4.1, supra.

#### 4.4.2 USE OF ANTISENSE OLIGONUCLEOTIDES FOR SUPPRESSION OF PROTEIN COMPLEX FORMATION OR PROTEIN COMPLEX/PROTEIN ACTIVITY

In a specific embodiment of the present invention, protein complex activity and formation and protein activity is inhibited by use of antisense nucleic acids for the component proteins of the complex, that inhibit transcription and/or translation of their complementary sequence. The present invention provides the therapeutic or prophylactic use of nucleic acids of at least six nucleotides that are antisense to a gene or cDNA encoding a component protein, or a portion thereof. An "antisense" nucleic acid as used herein refers to a nucleic acid capable of hybridizing to a sequence-specific portion of a component protein RNA (preferably mRNA) by virtue of some sequence complementarity. The antisense nucleic acid may be complementary to a coding and/or noncoding region of a component protein mRNA. Such antisense nucleic acids that inhibit complex formation or activity have utility as therapeutics, and can be used in the treatment or prevention of disorders as described supra.

The antisense nucleic acids of the invention can be oligonucleotides that are double-stranded or single-stranded, RNA or DNA, or a modification or derivative thereof, which can be directly administered to a cell, or which can be produced intracellularly by transcription of exogenous, introduced sequences.

In another embodiment, the present invention is directed to a method for inhibiting the expression of component protein nucleic acid sequences, in a prokaryotic or eukaryotic cell, comprising providing the cell with an effective amount of a composition comprising an antisense nucleic acid of the component protein, or a derivative thereof, of the invention.

The antisense nucleic acids are of at least six nucleotides and are preferably oligonucleotides, ranging from 6 to about 200 nucleotides. In specific aspects, the oligonucleotide is at least 10 nucleotides, at least 15 nucleotides, at least 100 nucleotides, or at least 200 nucleotides. The oligonucleotides can be DNA or RNA or chimeric mixtures, or derivatives or modified versions thereof, and either single-stranded or double-stranded. The oligonucleotide can be modified at the base moiety, sugar moiety, or phosphate backbone. The oligonucleotide may include other appending groups such as peptides, agents facilitating transport across the cell membrane (see, e.g., Letsinger et al., 1989, Proc. Natl. Acad. Sci. USA 86:6553-6556; Lemaitre et al., 1987, Proc. Natl. Acad. Sci. USA 84:648-652; International Patent Publication No. WO 88/09810) or blood-brain barrier (see, e.g., International Patent Publication No. WO 89/10134), hybridization-triggered cleavage agents (see, e.g., Krol et al., 1988, BioTechniques 6:958-976), or intercalating agents (see, e.g., Zon, 1988, Pharm. Res. 5:539-549).

In a preferred aspect of the invention, an antisense oligonucleotide is provided, preferably as single-stranded DNA. The oligonucleotide may be modified at any position in its structure with constituents generally known in the art.

The antisense oligonucleotides may comprise at least one modified base moiety which is selected from the group including but not limited to 5-fluorouracil, 5-bromouracil, 5-chlorouracil, 5-iodouracil, hypoxanthine, xanthine, 4-acetylcytosine, 5-(carboxyhydroxymethyl)uracil, 5-carboxymethylaminomethyl-2-thio-uridine, 5-carboxymethylaminomethyluracil, dihydrouracil,  $\beta$ -D-galactosylqueosine, inosine, N6-isopentenyladenine, 1-methylguanine, 1-methylinosine, 2,2-dimethylguanine, 2-methyladenine, 2-methylguanine, 3-methylcytosine, 5-methylcytosine, N6-adenine, 7-methylguanine, 5-methylaminomethyluracil, 5-methoxyaminomethyl-2-thiouracil,

$\beta$ -D-mannosylqueosine, 5N-methoxycarboxymethyluracil, 5-methoxyuracil, 2-methylthio-N6-isopentenyladenine, uracil-5-oxyacetic acid (v), wybutoxosine, pseudouracil, queosine, 2-thiocytosine, 5-methyl-2-thiouracil, 2-thiouracil, 4-thiouracil, 5-methyluracil, uracil-5-oxyacetic acid methylester, uracil-5-oxyacetic acid (v), 5-methyl-2-thiouracil, 3-(3-amino-3-N-2-carboxypropyl) uracil, (acp3)w, and 2,6-diaminopurine.

In another embodiment, the oligonucleotide comprises at least one modified sugar moiety selected from the group including, but not limited to, arabinose, 2-fluoroarabinose, xylulose, and hexose.

In yet another embodiment, the oligonucleotide comprises at least one modified phosphate backbone selected from the group consisting of a phosphorothioate, a phosphorodithioate, a phosphoramidothioate, a phosphoramidate, a phosphordiamidate, a methylphosphonate, an alkyl phosphotriester, and a formacetal, or an analog of the foregoing.

In yet another embodiment, the oligonucleotide is a 2'- $\alpha$ -anomeric oligonucleotide. An  $\alpha$ -anomeric oligonucleotide forms specific double-stranded hybrids with complementary RNA in which, contrary to the usual  $\beta$ -units, the strands run parallel to each other (Gautier et al., 1987, Nucl. Acids Res. 15:6625-6641).

The oligonucleotide may be conjugated to another molecule, e.g., a peptide, hybridization-triggered cross-linking agent, transport agent, hybridization-triggered cleavage agent, etc.

Oligonucleotides of the invention may be synthesized by standard methods known in the art, e.g., by use of an automated DNA synthesizer (such as are commercially available from Biosearch, Applied Biosystems, etc.). As examples, phosphorothioate oligo-nucleotides may be synthesized by the method of Stein et al. (1988, Nucl. Acids Res. 16:3209), methylphosphonate oligonucleotides can be prepared by use of controlled pore glass polymer supports (Sarin et al., 1988, Proc. Natl. Acad. Sci. USA 85:7448-7451), etc.

In a specific embodiment, the antisense oligonucleotides comprise catalytic RNAs, or ribozymes (see, e.g., International Patent Publication No. WO 90/11364; Sarver et al., 1990, Science 247:1222-1225). In another embodiment, the oligonucleotide is a 2'-0-methylribonucleotide (Inoue et al., 1987, Nucl. Acids Res. 15:6131-6148), or a chimeric RNA-DNA analog (Inoue et al., 1987, FEBS Lett. 215:327-330).

In an alternative embodiment, the antisense nucleic acids of the invention are produced intracellularly by transcription from an exogenous sequence. For example, a vector can be introduced *in vivo* such that it is taken up by a cell, within which cell the vector or a portion thereof is transcribed, producing an antisense nucleic acid (RNA) of the invention. Such a vector would contain a sequence encoding the component protein. Such a vector can remain episomal or become chromosomally integrated, as long as it can be transcribed to produce the desired antisense RNA. Such vectors can be constructed by recombinant DNA technology methods standard in the art. Vectors can be plasmid, viral, or others known in the art to be capable of replication and expression in mammalian cells. Expression of the sequences encoding the antisense RNAs can be by any promoter known in the art to act in mammalian, preferably human, cells. Such promoters can be inducible or constitutive. Such promoters include, but are not limited to, the SV40 early promoter region (Bernoist and Chambon, 1981, *Nature* 290:304-310), the promoter contained in the 3' long terminal repeat of Rous sarcoma virus (Yamamoto et al., 1980, *Cell* 22:787-797), the herpes thymidine kinase promoter (Wagner et al., 1981, *Proc. Natl. Acad. Sci. USA* 78:1441-1445), the regulatory sequences of the metallothionein gene (Brinster et al., 1982, *Nature* 296:39-42), etc.

The antisense nucleic acids of the invention comprise a sequence complementary to at least a portion of an RNA transcript of a component protein gene, preferably a human gene. However, absolute complementarity, although preferred, is not required. A sequence "complementary to at least a portion of an RNA," as referred to herein, means a sequence having sufficient complementarity to be able to hybridize with the RNA, forming a stable duplex; in the case of double-stranded antisense nucleic acids, a single strand of the duplex DNA may thus be tested, or triplex formation may be assayed. The ability to hybridize will depend on both the degree of complementarity and the length of the antisense nucleic acid. Generally, the longer the hybridizing nucleic acid, the more base mismatches with a component protein RNA it may contain and still form a stable duplex (or triplex, as the case may be). One skilled in the art can ascertain a tolerable degree of mismatch by use of standard procedures to determine the melting point of the hybridized complex.

The component protein antisense nucleic acids can be used to treat (or prevent) disorders of a cell type that expresses, or preferably overexpresses, a protein complex.

Cell types that express or overexpress component protein RNA can be identified by various methods known in the art. Such methods include, but are not limited to,

hybridization with component protein-specific nucleic acids (e.g., by Northern blot hybridization, dot blot hybridization, or *in situ* hybridization), or by observing the ability of RNA from the cell type to be translated *in vitro* into the component protein by immunohistochemistry, Western blot analysis, ELISA, etc. In a preferred aspect, primary tissue from a patient can be assayed for protein expression prior to treatment, e.g., by immunocytochemistry, *in situ* hybridization, or any number of methods to detect protein or mRNA expression.

Pharmaceutical compositions of the invention (see Section 4.7, *infra*), comprising an effective amount of a protein component antisense nucleic acid in a pharmaceutically acceptable carrier can be administered to a patient having a disease or disorder that is of a type that expresses or overexpresses a protein complex of the present invention.

The amount of antisense nucleic acid that will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. Where possible, it is desirable to determine the antisense cytotoxicity *in vitro*, and then in useful animal model systems, prior to testing and use in humans.

In a specific embodiment, pharmaceutical compositions comprising antisense nucleic acids are administered via liposomes, microparticles, or microcapsules. In various embodiments of the invention, it may be useful to use such compositions to achieve sustained release of the antisense nucleic acids. In a specific embodiment, it may be desirable to utilize liposomes targeted via antibodies to specific identifiable central nervous system cell types (Leonetti et al., 1990, Proc. Natl. Acad. Sci. U.S.A. 87:2448-2451; Renneisen et al., 1990, J. Biol. Chem. 265:16337-16342).

#### 4.5 ASSAYS OF PROTEIN COMPLEXES/PROTEINS OF THE INVENTION AND DERIVATIVES AND ANALOGS THEREOF

The functional activity of a protein complex of the present invention, or a derivative, fragment or analog thereof or protein component thereof, can be assayed by various methods. Potential modulators (e.g., agonists and antagonists) of complex activity or formation, e.g., anti- complex antibodies and antisense nucleic acids, can be assayed for the ability to modulate complex activity or formation.

In one embodiment of the present invention, where one is assaying for the ability to bind or compete with a wild-type complex for binding to an anti-complex antibody, various immunoassays known in the art can be used, including but not limited to competitive and non-competitive assay systems using techniques such as radioimmunoassay, ELISA (enzyme linked immunosorbent assay), "sandwich" immunoassays, immunoradiometric assays, gel diffusion precipitin reactions, immunodiffusion assays, in situ immunoassays (using colloidal gold, enzyme or radioisotope labels), western blot analysis, precipitation reactions, agglutination assays (e.g., gel agglutination assays, hemagglutination assays), complement fixation assays, immunofluorescence assays, protein A assays, immunoelectrophoresis assays, etc. In one embodiment, antibody binding is detected by detecting a label on the primary antibody. In another embodiment, the primary antibody is detected by detecting binding of a secondary antibody or reagent to the primary antibody. In a further embodiment, the secondary antibody is labeled. Many means are known in the art for detecting binding in an immunoassay and are within the scope of the present invention.

The expression of the component protein genes (both endogenous and those expressed from cloned DNA containing the genes) can be detected using techniques known in the art, including but not limited to Southern hybridization (Southern, 1975, J. Mol. Biol. 98:503-517), northern hybridization (see, e.g., Freeman et al., 1983, Proc. Natl. Acad. Sci. USA 80:4094-4098), restriction endonuclease mapping (Sambrook et al., 1989, Molecular Cloning, A Laboratory Manual, 2<sup>nd</sup> Ed. Cold Spring Harbor Laboratory Press, New York), RNase protection assays (Current Protocols in Molecular Biology, John Wiley and Sons, New York, 1997), DNA sequence analysis, and polymerase chain reaction amplification (PCR; U.S. Patent Nos. 4,683,202, 4,683,195, and 4,889,818; Gyllenstein et al., 1988, Proc. Natl. Acad. Sci. USA 85:7652-7657; Ochman et al., 1988, Genetics 120:621-623; Loh et al., 1989, Science 243:217-220) followed by Southern hybridization with probes specific for the component protein genes, in various cell types. Methods of amplification other than PCR commonly known in the art can be employed. In one embodiment, Southern hybridization can be used to detect genetic linkage of component protein gene mutations to physiological or pathological states. Various cell types, at various stages of development, can be characterized for their expression of component proteins at the same time and in the same cells. The stringency of the hybridization conditions for northern or Southern blot analysis can be manipulated to ensure detection of nucleic acids with the desired degree of relatedness to the specific

probes used. Modifications to these methods and other methods commonly known in the art can be used.

Derivatives (e.g., fragments), homologs and analogs of one component protein can be assayed for binding to another component protein in the same complex by any method known in the art, for example the modified yeast matrix mating test described in Section 4.6.1 infra, immunoprecipitation with an antibody that binds to the component protein complexed with other component proteins in the same complex, followed by size fractionation of the immunoprecipitated proteins (e.g., by denaturing or nondenaturing polyacrylamide gel electrophoresis), Western blot analysis, etc.

One embodiment of the invention provides a method for screening a derivative, homolog or analog of a component protein for biological activity comprising contacting said derivative, homolog or analog of the component protein with the other component proteins in the same complex; and detecting the formation of a complex between said derivative, homolog or analog of the component protein and the other component proteins; wherein detecting formation of said complex indicates that said derivative, homolog or analog of has biological (e.g., binding) activity.

The invention also provides methods of modulating the activity of a component protein that can participate in a protein complex by administration of a binding partner of that protein or derivative, homolog or analog thereof.

In a specific embodiment of the present invention, a protein complex of the present invention is administered to treat or prevent a disease or disorder, since the complex and/or component proteins have been implicated in the disease and disorder. Accordingly, a protein complex or a derivative, homolog, analog or fragment thereof, nucleic acids encoding the component proteins, anti-complex antibodies, and other modulators of protein complex activity, can be tested for activity in treating or preventing a disease or disorder in *in vitro* and *in vivo* assays.

In one embodiment, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by contacting cultured cells that exhibit an indicator of the disease *in vitro*, with the therapeutic, and comparing the level of said indicator in the cells contacted with the therapeutic, with said level of said indicator in cells not so contacted, wherein a lower level in said contacted cells indicates that the therapeutic has activity in treating or preventing the disease.

In another embodiment of the invention, a therapeutic of the invention can be assayed for activity in treating or preventing a disease by administering the therapeutic to

a test animal that is predisposed to develop symptoms of a disease, and measuring the change in said symptoms of the disease after administration of said therapeutic, wherein a reduction in the severity of the symptoms of the disease or prevention of the symptoms of the disease indicates that the therapeutic has activity in treating or preventing the disease. Such a test animal can be any one of a number of animal models known in the art for disease. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention.

#### 4.6 SCREENING FOR MODULATORS OF THE PROTEIN COMPLEXES/PROTEINS OF THE INVENTION

A complex of the present invention, the component proteins of the complex and nucleic acids encoding the component proteins, as well as derivatives and fragments of the amino and nucleic acids, can be used to screen for compounds that bind to, or modulate the amount of, activity of, or protein component composition of, said complex, and thus, have potential use as modulators, i.e., agonists or antagonists, of complex activity, and/or complex formation, i.e., the amount of complex formed, and/or protein component composition of the complex.

Thus, the present invention is also directed to methods for screening for molecules that bind to, or modulate the function of, amount of, activity of, formation of or protein component composition of, a complex of the present invention. In one embodiment of the invention, the method for screening for a molecule that modulates directly or indirectly the function, activity or formation of a complex of the present invention comprises exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules under conditions conducive to modulation; and determining the amount of, the biochemical activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependend on the complex and/or the abundance and/or activity of a protein or protein complex dependend on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular

localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

In a further specific embodiment, a modulation of the formation process of a complex can be determined.

Such a modulation can either be a change in the typical time course of its formation or a change in the typical steps leading to the formation of the complete complex.

Such changes can for example be detected by analysing and comparing the process of complex formation in untreated wild type cells of a particular type and/or cells showing or having the predisposition to develop a certain disease phenotype and/or cells which have been treated with particular conditions and/or particular agents in a particular situation. Methods to study such changes in time course are well known in the art and include for example Western-blot analysis of the proteins in the complex isolated at different steps of its formation.

Furthermore an aberrant intracellular localization of the protein complex and/or an aberrant transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or a gene dependent on the complex can serve as a marker for a disease and thus have diagnostic utility for any disease which is caused by an aberrant activity, function, composition or formation of the complex of the invention.

Methods to study the intracellular localization are well known in the art and include, but are not limited to immunofluorescence analysis using antibodies specific for components of the protein. Preferentially, double-stainings including staining of other cellular structures are being used to facilitate the detection of the intracellular localization. Methods to analyse the transcription levels of a gene dependent on the complex are also well known in the art and include Northern blot analysis, quantitative PCR etc. The abundance of proteins dependent on the protein can be analyzed as described supra. Methods to study changes in the activity of proteins dependent on complex depend on the protein. The choice of such methods will be apparent to any person skilled in the art.

In another embodiment, the present invention further relates to a process for the identification and/or preparation of an effector of the complex comprising the step of

bringing into contact a product of any of claims 1 to 8 with a compound, a mixture or a library of compounds and determining whether the compound or a certain compound of the mixture or library binds to the product and/or effects the products biological activity and optionally further purifying the compound positively tested as effector.

In another embodiment, the present invention is directed to a method for screening for a molecule that binds a protein complex of the present invention comprising exposing said complex, or a cell or organism containing the complex machinery, to one or more candidate molecules; and determining whether said complex is bound by any of said candidate molecules. Such screening assays can be carried out using cell-free and cell-based methods that are commonly known in the art in vitro, in vivo or ex vivo. For example, an isolated complex can be employed, or a cell can be contacted with the candidate molecule and the complex can be isolated from such contacted cells and the isolated complex can be assayed for activity or component composition. In another example, a cell containing the complex can be contacted with the candidate molecule and the levels of the complex in the contacted cell can be measured. Additionally, such assays can be carried out in cells recombinantly expressing a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, and a component protein from fifth column of table 1, or a functionally active fragment or functionally active derivative thereof. Additionally, such assays can also be carried out in cells recombinantly expressing all component proteins from the group of proteins in the fifth column of table 1.

For example, assays can be carried out using recombinant cells expressing the protein components of a complex, to screen for molecules that bind to, or interfere with, or promote complex activity or formation. In preferred embodiments, polypeptide derivatives that have superior stabilities but retain the ability to form a complex (e.g., one or more component proteins modified to be resistant to proteolytic degradation in the binding assay buffers, or to be resistant to oxidative degradation), are used to screen for modulators of complex activity or formation. Such resistant molecules can be generated, e.g., by substitution of amino acids at proteolytic cleavage sites, the use of chemically derivatized amino acids at proteolytic susceptible sites, and the replacement of amino acid residues subject to oxidation, i.e. methionine and cysteine.

A particular aspect of the present invention relates to identifying molecules that inhibit or promote formation or degradation of a complex of the present invention, e.g.,

using the method described for isolating the complex and identifying members of the complex using the TAP assay described in Section 4, *infra*, and in WO 00/09716 and Rigaut et al., 1999, *Nature Biotechnol.* 17:1030-1032, which are each incorporated by reference in their entirety. TNRF1

In another embodiment of the invention, a modulator is identified by administering a candidate molecule to a transgenic non-human animal expressing the complex component proteins from promoters that are not the native promoters of the respective proteins, more preferably where the candidate molecule is also recombinantly expressed in the transgenic non-human animal. Alternatively, the method for identifying such a modulator can be carried out *in vitro*, preferably with a purified complex, and a purified candidate molecule.

Agents/molecules (candidate molecules) to be screened can be provided as mixtures of a limited number of specified compounds, or as compound libraries, peptide libraries and the like. Agents/molecules to be screened may also include all forms of antisera, antisense nucleic acids, etc., that can modulate complex activity or formation. Exemplary candidate molecules and libraries for screening are set forth in Section 4.6.1, *infra*.

Screening the libraries can be accomplished by any of a variety of commonly known methods. See, e.g., the following references, which disclose screening of peptide libraries: Parmley and Smith, 1989, *Adv. Exp. Med. Biol.* 251:215-218; Scott and Smith, 1990, *Science* 249:386-390; Fowlkes et al., 1992, *BioTechniques* 13:422-427; Oldenburg et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:5393-5397; Yu et al., 1994, *Cell* 76:933-945; Staudt et al., 1988, *Science* 241:577-580; Bock et al., 1992, *Nature* 355:564-566; Tuerk et al., 1992, *Proc. Natl. Acad. Sci. USA* 89:6988-6992; Ellington et al., 1992, *Nature* 355:850-852; U.S. Patent No. 5,096,815, U.S. Patent No. 5,223,409, and U.S. Patent No. 5,198,346, all to Ladner et al.; Rebar and Pabo, 1993, *Science* 263:671-673; and International Patent Publication No. WO 94/18318.

In a specific embodiment, screening can be carried out by contacting the library members with a complex immobilized on a solid phase, and harvesting those library members that bind to the protein (or encoding nucleic acid or derivative). Examples of such screening methods, termed "panning" techniques, are described by way of example in Parmley and Smith, 1988, *Gene* 73:305-318; Fowlkes et al., 1992, *BioTechniques* 13:422-427; International Patent Publication No. WO 94/18318; and in references cited hereinabove.

In a specific embodiment, fragments and/or analogs of protein components of a complex, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex formation (amount of complex or composition of complex) or activity in the cell, which thereby inhibit complex activity or formation in the cell.

In one embodiment, agents that modulate (i.e., antagonize or agonize) complex activity or formation can be screened for using a binding inhibition assay, wherein agents are screened for their ability to modulate formation of a complex under aqueous, or physiological, binding conditions in which complex formation occurs in the absence of the agent to be tested. Agents that interfere with the formation of complexes of the invention are identified as antagonists of complex formation. Agents that promote the formation of complexes are identified as agonists of complex formation. Agents that completely block the formation of complexes are identified as inhibitors of complex formation.

Methods for screening may involve labeling the component proteins of the complex with radioligands (e.g.,  $^{125}\text{I}$  or  $^3\text{H}$ ), magnetic ligands (e.g., paramagnetic beads covalently attached to photobiotin acetate), fluorescent ligands (e.g., fluorescein or rhodamine), or enzyme ligands (e.g., luciferase or  $\beta$ -galactosidase). The reactants that bind in solution can then be isolated by one of many techniques known in the art, including but not restricted to, co-immunoprecipitation of the labeled complex moiety using antisera against the unlabeled binding partner (or labeled binding partner with a distinguishable marker from that used on the second labeled complex moiety), immunoaffinity chromatography, size exclusion chromatography, and gradient density centrifugation. In a preferred embodiment, the labeled binding partner is a small fragment or peptidomimetic that is not retained by a commercially available filter. Upon binding, the labeled species is then unable to pass through the filter, providing for a simple assay of complex formation.

Methods commonly known in the art are used to label at least one of the component members of the complex. Suitable labeling methods include, but are not limited to, radiolabeling by incorporation of radiolabeled amino acids, e.g.,  $^3\text{H}$ -leucine or  $^{35}\text{S}$ -methionine, radiolabeling by post-translational iodination with  $^{125}\text{I}$  or  $^{131}\text{I}$  using the chloramine T method, Bolton-Hunter reagents, etc., or labeling with  $^{32}\text{P}$  using phosphorylase and inorganic radiolabeled phosphorous, biotin labeling with photobiotin-acetate and sunlamp exposure, etc. In cases where one of the members of the complex is immobilized, e.g., as described infra, the free species is labeled. Where neither of the

interacting species is immobilized, each can be labeled with a distinguishable marker such that isolation of both moieties can be followed to provide for more accurate quantification, and to distinguish the formation of homomeric from heteromeric complexes. Methods that utilize accessory proteins that bind to one of the modified interactants to improve the sensitivity of detection, increase the stability of the complex, etc., are provided.

Typical binding conditions are, for example, but not by way of limitation, in an aqueous salt solution of 10-250 mM NaCl, 5-50 mM Tris-HCl, pH 5-8, and 0.5% Triton X-100 or other detergent that improves specificity of interaction. Metal chelators and/or divalent cations may be added to improve binding and/or reduce proteolysis. Reaction temperatures may include 4, 10, 15, 22, 25, 35, or 42 degrees Celsius, and time of incubation is typically at least 15 seconds, but longer times are preferred to allow binding equilibrium to occur. Particular complexes can be assayed using routine protein binding assays to determine optimal binding conditions for reproducible binding.

The physical parameters of complex formation can be analyzed by quantification of complex formation using assay methods specific for the label used, e.g., liquid scintillation counting for radioactivity detection, enzyme activity for enzyme-labeled moieties, etc. The reaction results are then analyzed utilizing Scatchard analysis, Hill analysis, and other methods commonly known in the arts (see, e.g., Proteins, Structures, and Molecular Principles, 2<sup>nd</sup> Edition (1993) Creighton, Ed., W.H. Freeman and Company, New York).

In a second common approach to binding assays, one of the binding species is immobilized on a filter, in a microtiter plate well, in a test tube, to a chromatography matrix, etc., either covalently or non-covalently. Proteins can be covalently immobilized using any method well known in the art, for example, but not limited to the method of Kadonaga and Tjian, 1986, Proc. Natl. Acad. Sci. USA 83:5889-5893, i.e., linkage to a cyanogen-bromide derivatized substrate such as CNBr-Sepharose 4B (Pharmacia). Where needed, the use of spacers can reduce steric hindrance by the substrate. Non-covalent attachment of proteins to a substrate include, but are not limited to, attachment of a protein to a charged surface, binding with specific antibodies, binding to a third unrelated interacting protein, etc.

Assays of agents (including cell extracts or a library pool) for competition for binding of one member of a complex (or derivatives thereof) with another member of the

complex labeled by any means (e.g., those means described above) are provided to screen for competitors or enhancers of complex formation.

In specific embodiments, blocking agents to inhibit non-specific binding of reagents to other protein components, or absorptive losses of reagents to plastics, immobilization matrices, etc., are included in the assay mixture. Blocking agents include, but are not restricted to bovine serum albumin,  $\beta$ -casein, nonfat dried milk, Denhardt's reagent, Ficoll, polyvinylpyrrolidine, nonionic detergents (NP40, Triton X-100, Tween 20, Tween 80, etc.), ionic detergents (e.g., SDS, LDS, etc.), polyethylene glycol, etc. Appropriate blocking agent concentrations allow complex formation.

After binding is performed, unbound, labeled protein is removed in the supernatant, and the immobilized protein retaining any bound, labeled protein is washed extensively. The amount of bound label is then quantified using standard methods in the art to detect the label as described, supra.

In another specific embodiment screening for modulators of the protein complexes/protein as provided herein can be carried out by attaching those and/or the antibodies as provided herein to a solid carrier. In a further specific embodiment, the invention relates to an array of said molecules.

The preparation of such an array containing different types of proteins, including antibodies) is well known in the art and is apparent to a person skilled in the art (see e.g. Ekins et al., 1989, J. Pharm. Biomed. Anal. 7:155-168; Mitchell et al. 2002, Nature Biotechnol. 20:225-229; Petricoin et al., 2002, Lancet 359:572-577; Templin et al., 2001, Trends Biotechnol. 20:160-166; Wilson and Nock, 2001, Curr. Opin. Chem. Biol. 6:81-85; Lee et al., 2002 Science 295:1702-1705; MacBeath and Schreiber, 2000, Science 289:1760; Blawas and Reichert, 1998, Biomaterials 19:595; Kane et al., 1999, Biomaterials 20:2363; Chen et al., 1997, Science 276:1425; Vaughan et al., 1996, Nature Biotechnol. 14:309-314; Mahler et al., 1997, Immunotechnology 3:31-43; Roberts et al., 1999, Curr. Opin. Chem. Biol. 3:268-273; Nord et al., 1997, Nature Biotechnol. 15:772-777; Nord et al., 2001, Eur. J. Biochem. 268:4269-4277; Brody and Gold, 2000, Rev. Mol. Biotechnol. 74:5-13; Karlstroem and Nygren, 2001, Anal. Biochem. 295:22-30; Nelson et al., 2000, Electrophoresis 21:1155-1163; Honore et al., 2001, Expert Rev. Mol. Diagn. 3:265-274; Albala, 2001, Expert Rev. Mol. Diagn. 2:145-152, Figeys and Pinto, 2001, Electrophoresis 2:208-216 and references in the publications listed here).

Complexes can be attached to an array by different means as will be apparent to a person skilled in the art. Complexes can for example be added to the array via a TAP-

tag (as described in WO/0009716 and in Rigaut et al., 1999, *Nature Biotechnol.* 10:1030-1032) after the purification step or by another suitable purification scheme as will be apparent to a person skilled in the art.

Optionally, the proteins of the complex can be cross-linked to enhance the stability of the complex. Different methods to cross-link proteins are well known in the art. Reactive end-groups of cross-linking agents include but are not limited to -COOH, -SH, -NH<sub>2</sub> or N-oxy-succinamate.

The spacer of the cross-linking agent should be chosen with respect to the size of the complex to be cross-linked. For small protein complexes, comprising only a few proteins, relatively short spacers are preferable in order to reduce the likelihood of cross-linking separate complexes in the reaction mixture. For larger protein complexes, additional use of larger spacers is preferable in order to facilitate cross-linking between proteins within the complex.

It is preferable to check the success-rate of cross-linking before linking the complex to the carrier.

As will be apparent to a person skilled in the art, the optimal rate of cross-linking need to be determined on a case by case basis. This can be achieved by methods well known in the art, some of which are exemplary described below.

A sufficient rate of cross-linking can be checked f.e. by analysing the cross-linked complex vs. a non-cross-linked complex on a denaturing protein gel.

If cross-linking has been performed successfully, the proteins of the complex are expected to be found in the same lane, whereas the proteins of the non-cross-linked complex are expected to be separated according to their individual characteristics. Optionally the presence of all proteins of the complex can be further checked by peptide-sequencing of proteins in the respective bands using methods well known in the art such as mass spectrometry and/or Edman degradation.

In addition, a rate of crosslinking which is too high should also be avoided. If cross-linking has been carried out too extensively, there will be an increasing amount of cross-linking of the individual protein complex, which potentially interferes with a screening for potential binding partners and/or modulators etc. using the arrays.

The presence of such structures can be determined by methods well known in the art and include e.g. gel-filtration experiments comparing the gel filtration profile solutions containing cross-linked complexes vs. uncross-linked complexes.

Optionally, functional assays as will be apparent to a person skilled in the art, some of which are exemplarily provided herein, can be performed to check the integrity of the complex.

Alternatively, members of the protein complex can be expressed as a single fusion protein and coupled to the matrix as will be apparent to a person skilled in the art.

Optionally, the attachment of the complex or proteins or antibody as outlined above can be further monitored by various methods apparent to a person skilled in the art. Those include, but are not limited to surface plasmon resonance (see e.g. McDonnel, 2001, Curr. Opin. Chem. Biol. 5:572-577; Lee, 2001, Trends Biotechnol. 19:217-222; Weinberger et al., 2000, 1:395-416; Pearson et al., 2000, Ann. Clin. Biochem. 37:119-145; Vely et al., 2000, Methods Mol. Biol. 121:313-321; Slepak, 2000, J. Mol Recognit. 13:20-26.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the gamma-secretase activity in vitro of the Presenilin 1 complex include but are not limited to those described in Li Y M et al., 2000, Proc Natl Acad Sci U S A, 97:6138-43 and Pinnix I et al., 2001, J Biol Chem, 276:481-7.

Exemplary assays useful for measuring the gamma-secretase dependent transcriptional activity of the Presenilin 1 complex include but are not limited to those described in Karlstrom H et al., 2002, J Biol Chem, 277:6763-6.

Exemplary assays useful for measuring the formation of amyloid-beta peptides and their aggregated forms of the Presenilin 1 complex include but are not limited to those described in De Strooper B et al., 1998, *Nature*, 391:387-90.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex, include but are not limited to those described in Yan R et al., 1999, *Nature*, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex, include but are not limited to those described in Tian G et al., 2002, *J Biol Chem*, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1-complex, BACE2-complex, APP-complex, APP-C99-complex, APP-C59-complex, Psen-1-complex, Psen-2-complex, Nicastin-complex, Aph-1a-complex, Pen-2-complex, CtnnB1-complex, X11-beta-complex, Fe65-complex, Fe65L2-complex, DAB1-complex, JIP1-complex, TIP60-complex, GSK3a-complex, Tau-complex, FKRP-complex, PTK7-complex, include but are not limited to those described in Cao X et al., 2001, *Science*, 293:115-20.

Exemplary assays useful for measuring the phosphorylation of Tau proteins in vitro or in cells (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of

the Tau complex include but are not limited to those described in Drewes G et al., 1997, Cell, 89:297-308.

Exemplary assays useful for measuring the aggregation of Tau proteins into filaments or tangles in vitro or in cells (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Tau complex include but are not limited to those described in Barghorn S et al., 2000, Biochemistry, 39:11714-21.

Exemplary assays useful for measuring the transactivation of reporter genes by APP-Gal4/VP16 (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11beta complex include but are not limited to those described in Biederer T et al., 2002, J Neurosci, 22:7340-51.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring the transactivation of reporter genes by APP-Gal4/VP16 (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Biederer Thomas et al., 2002, J Neurosci, 22:7340-51.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the X11b-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PSEN2 -complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PSEN2 -complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting of the PSEN2 -complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the PSEN2 -complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Nicastrin-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Aph-1a-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Aph-1a-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Aph-1a-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Aph-1a-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pen-2-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pen-2-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the Pen-2-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Pen-2-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-C99 -complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the DAB1-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the DAB1-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting of the DAB1-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the DAB1-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the JIP1-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting

proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Fe65L2-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Neurotrypsin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the Telencephalin-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BACE1 (new)-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE1 (new)-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Vassar R et al., 1999, Science, 286:735-41.

Exemplary assays useful for measuring the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the BACE2-complex include but are not limited to those described in Yan R et al., 1999, Nature, 402:533-7.

Exemplary assays useful for measuring the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting of the BACE2-complex include but are not limited to those described in Tian Gaochao et al., 2002, J Biol Chem, 277:31499-505.

Exemplary assays useful for measuring transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) of the APP-

C59-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring transcriptional activity in vivo of the Tip60-complex include but are not limited to those described in Cao X et al., 2001, Science, 293:115-20.

Exemplary assays useful for measuring Apoptotic activity of the Tip60-complex include but are not limited to those described in Kinoshita Ayae et al., 2002, J Biol Chem, 277:28530-6.

#### 4.6.1 CANDIDATE MOLECULES

Any molecule known in the art can be tested for its ability to modulate (increase or decrease) the amount of, activity of, or protein component composition of a complex of the present invention as detected by a change in the amount of, activity of, or protein component composition of, said complex. By way of example, a change in the amount of the complex can be detected by detecting a change in the amount of the complex that can be isolated from a cell expressing the complex machinery. For identifying a molecule that modulates complex activity, candidate molecules can be directly provided to a cell expressing the complex machinery, or, in the case of candidate proteins, can be provided by providing their encoding nucleic acids under conditions in which the nucleic acids are recombinantly expressed to produce the candidate proteins within the cell expressing the complex machinery, the complex is then isolated from the cell and the isolated complex is assayed for activity using methods well known in the art, not limited to those described, supra.

This embodiment of the invention is well suited to screen chemical libraries for molecules which modulate, e.g., inhibit, antagonize, or agonize, the amount of, activity of, or protein component composition of the complex. The chemical libraries can be peptide libraries, peptidomimetic libraries, chemically synthesized libraries, recombinant, e.g., phage display libraries, and in vitro translation-based libraries, other non-peptide synthetic organic libraries, etc.

Exemplary libraries are commercially available from several sources (ArQule, Tripos/PanLabs, ChemDesign, Pharmacopoeia). In some cases, these chemical libraries are generated using combinatorial strategies that encode the identity of each

member of the library on a substrate to which the member compound is attached, thus allowing direct and immediate identification of a molecule that is an effective modulator. Thus, in many combinatorial approaches, the position on a plate of a compound specifies that compound's composition. Also, in one example, a single plate position may have from 1-20 chemicals that can be screened by administration to a well containing the interactions of interest. Thus, if modulation is detected, smaller and smaller pools of interacting pairs can be assayed for the modulation activity. By such methods, many candidate molecules can be screened.

Many diversity libraries suitable for use are known in the art and can be used to provide compounds to be tested according to the present invention. Alternatively, libraries can be constructed using standard methods. Chemical (synthetic) libraries, recombinant expression libraries, or polysome-based libraries are exemplary types of libraries that can be used.

The libraries can be constrained or semirigid (having some degree of structural rigidity), or linear or nonconstrained. The library can be a cDNA or genomic expression library, random peptide expression library or a chemically synthesized random peptide library, or non-peptide library. Expression libraries are introduced into the cells in which the assay occurs, where the nucleic acids of the library are expressed to produce their encoded proteins.

In one embodiment, peptide libraries that can be used in the present invention may be libraries that are chemically synthesized in vitro. Examples of such libraries are given in Houghten et al., 1991, *Nature* 354:84-86, which describes mixtures of free hexapeptides in which the first and second residues in each peptide were individually and specifically defined; Lam et al., 1991, *Nature* 354:82-84, which describes a "one bead, one peptide" approach in which a solid phase split synthesis scheme produced a library of peptides in which each bead in the collection had immobilized thereon a single, random sequence of amino acid residues; Medynski, 1994, *Bio/Technology* 12:709-710, which describes split synthesis and T-bag synthesis methods; and Gallop et al., 1994, *J. Med. Chem.* 37:1233-1251. Simply by way of other examples, a combinatorial library may be prepared for use, according to the methods of Ohlmeyer et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:10922-10926; Erb et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:11422-11426; Houghten et al., 1992, *Biotechniques* 13:412; Jayawickreme et al., 1994, *Proc. Natl. Acad. Sci. USA* 91:1614-1618; or Salmon et al., 1993, *Proc. Natl. Acad. Sci. USA* 90:11708-11712. PCT Publication No. WO 93/20242 and Brenner and Lerner,

1992, Proc. Natl. Acad. Sci. USA 89:5381-5383 describe "encoded combinatorial chemical libraries," that contain oligonucleotide identifiers for each chemical polymer library member.

In a preferred embodiment, the library screened is a biological expression library that is a random peptide phage display library, where the random peptides are constrained (e.g., by virtue of having disulfide bonding).

Further, more general, structurally constrained, organic diversity (e.g., nonpeptide) libraries, can also be used. By way of example, a benzodiazepine library (see e.g., Bunin et al., 1994, Proc. Natl. Acad. Sci. USA 91:4708-4712) may be used.

Conformationally constrained libraries that can be used include but are not limited to those containing invariant cysteine residues which, in an oxidizing environment, cross-link by disulfide bonds to form cystines, modified peptides (e.g., incorporating fluorine, metals, isotopic labels, are phosphorylated, etc.), peptides containing one or more non-naturally occurring amino acids, non-peptide structures, and peptides containing a significant fraction of -carboxyglutamic acid.

Libraries of non-peptides, e.g., peptide derivatives (for example, that contain one or more non-naturally occurring amino acids) can also be used. One example of these are peptoid libraries (Simon et al., 1992, Proc. Natl. Acad. Sci. USA 89:9367-9371). Peptoids are polymers of non-natural amino acids that have naturally occurring side chains attached not to the  $\alpha$  carbon but to the backbone amino nitrogen. Since peptoids are not easily degraded by human digestive enzymes, they are advantageously more easily adaptable to drug use. Another example of a library that can be used, in which the amide functionalities in peptides have been permethylated to generate a chemically transformed combinatorial library, is described by Ostresh et al., 1994, Proc. Natl. Acad. Sci. USA 91:11138-11142).

The members of the peptide libraries that can be screened according to the invention are not limited to containing the 20 naturally occurring amino acids. In particular, chemically synthesized libraries and polysome based libraries allow the use of amino acids in addition to the 20 naturally occurring amino acids (by their inclusion in the precursor pool of amino acids used in library production). In specific embodiments, the library members contain one or more non-natural or non-classical amino acids or cyclic peptides. Non-classical amino acids include but are not limited to the D-isomers of the common amino acids, -amino isobutyric acid, 4-aminobutyric acid, Abu, 2-amino butyric acid; -Abu, -Ahx, 6-amino hexanoic acid; Aib, 2-amino isobutyric acid; 3-amino propionic acid;

acid; ornithine; norleucine; norvaline, hydroxyproline, sarcosine, citrulline, cysteic acid, t-butylglycine, t-butylalanine, phenylglycine, cyclohexylalanine,  $\beta$ -alanine, designer amino acids such as  $\beta$ -methyl amino acids, C-methyl amino acids, N-methyl amino acids, fluoro-amino acids and amino acid analogs in general. Furthermore, the amino acid can be D (dextrorotary) or L (levorotary).

In a specific embodiment, fragments and/or analogs of complexes of the invention, or protein components thereof, especially peptidomimetics, are screened for activity as competitive or non-competitive inhibitors of complex activity or formation.

In another embodiment of the present invention, combinatorial chemistry can be used to identify modulators of the complexes. Combinatorial chemistry is capable of creating libraries containing hundreds of thousands of compounds, many of which may be structurally similar. While high throughput screening programs are capable of screening these vast libraries for affinity for known targets, new approaches have been developed that achieve libraries of smaller dimension but which provide maximum chemical diversity. (See e.g., Matter, 1997, J. Med. Chem. 40:1219-1229).

One method of combinatorial chemistry, affinity fingerprinting, has previously been used to test a discrete library of small molecules for binding affinities for a defined panel of proteins. The fingerprints obtained by the screen are used to predict the affinity of the individual library members for other proteins or receptors of interest (in the instant invention, the protein complexes of the present invention and protein components thereof.) The fingerprints are compared with fingerprints obtained from other compounds known to react with the protein of interest to predict whether the library compound might similarly react. For example, rather than testing every ligand in a large library for interaction with a complex or protein component, only those ligands having a fingerprint similar to other compounds known to have that activity could be tested. (See, e.g., Kauvar et al., 1995, Chem. Biol. 2:107-118; Kauvar, 1995, Affinity fingerprinting, Pharmaceutical Manufacturing International. 8:25-28; and Kauvar, Toxic-Chemical Detection by Pattern Recognition in New Frontiers in Agrochemical Immunoassay, Kurtz, Stanker and Skerritt (eds), 1995, AOAC: Washington, D.C., 305-312).

Kay et al. (1993, Gene 128:59-65) disclosed a method of constructing peptide libraries that encode peptides of totally random sequence that are longer than those of any prior conventional libraries. The libraries disclosed in Kay et al. encode totally synthetic random peptides of greater than about 20 amino acids in length. Such libraries can be advantageously screened to identify complex modulators. (See also U.S. Patent

No. 5,498,538 dated March 12, 1996; and PCT Publication No. WO 94/18318 dated August 18, 1994).

A comprehensive review of various types of peptide libraries can be found in Gallop et al., 1994, J. Med. Chem. 37:1233-1251.

#### 4.7 PHARMACEUTICAL COMPOSITIONS AND THERAPEUTIC/PROPHYLACTIC ADMINISTRATION

The invention provides methods of treatment (and prophylaxis) by administration to a subject of an effective amount of a therapeutic of the invention. In a preferred aspect, the therapeutic is substantially purified. The subject is preferably an animal including, but not limited to animals such as cows, pigs, horses, chickens, cats, dogs, etc., and is preferably a mammal, and most preferably human. In a specific embodiment, a non-human mammal is the subject.

Various delivery systems are known and can be used to administer a therapeutic of the invention, e.g., encapsulation in liposomes, microparticles, and microcapsules; use of recombinant cells capable of expressing the therapeutic, use of receptor-mediated endocytosis (e.g., Wu and Wu, 1987, J. Biol. Chem. 262:4429-4432); construction of a therapeutic nucleic acid as part of a retroviral or other vector, etc. Methods of introduction include but are not limited to intradermal, intramuscular, intraperitoneal, intravenous, subcutaneous, intranasal, epidural, and oral routes. The compounds may be administered by any convenient route, for example by infusion, by bolus injection, by absorption through epithelial or mucocutaneous linings (e.g., oral, rectal and intestinal mucosa, etc.), and may be administered together with other biologically active agents. Administration can be systemic or local. In addition, it may be desirable to introduce the pharmaceutical compositions of the invention into the central nervous system by any suitable route, including intraventricular and intrathecal injection; intraventricular injection may be facilitated by an intraventricular catheter, for example, attached to a reservoir, such as an Ommaya reservoir. Pulmonary administration can also be employed, e.g., by use of an inhaler or nebulizer, and formulation with an aerosolizing agent.

In a specific embodiment, it may be desirable to administer the pharmaceutical compositions of the invention locally to the area in need of treatment. This may be achieved by, for example, and not by way of limitation, local infusion during surgery,

topical application, e.g., in conjunction with a wound dressing after surgery, by injection, by means of a catheter, by means of a suppository, or by means of an implant, said implant being of a porous, non-porous, or gelatinous material, including membranes, such as sialastic membranes, or fibers. In one embodiment, administration can be by direct injection at the site (or former site) of a malignant tumor or neoplastic or pre-neoplastic tissue.

In another embodiment, the therapeutic can be delivered in a vesicle, in particular a liposome (Langer, 1990, *Science* 249:1527-1533; Treat et al., 1989, In: *Liposomes in the Therapy of Infectious Disease and Cancer*, Lopez-Berestein and Fidler, eds., Liss, New York, pp. 353-365; Lopez-Berestein, *ibid.*, pp. 317-327; see generally *ibid.*)

In yet another embodiment, the therapeutic can be delivered via a controlled release system. In one embodiment, a pump may be used (Langer, *supra*; Sefton, 1987, *CRC Crit. Ref. Biomed. Eng.* 14:201-240; Buchwald et al., 1980, *Surgery* 88:507-516; Saudek et al., 1989, *N. Engl. J. Med.* 321:574-579). In another embodiment, polymeric materials can be used (*Medical Applications of Controlled Release*, Langer and Wise, eds., CRC Press, Boca Raton, Florida, 1974; *Controlled Drug Bioavailability, Drug Product Design and Performance*, Smolen and Ball, eds., Wiley, New York, 1984; Ranger and Peppas, 1983, *Macromol. Sci. Rev. Macromol. Chem.* 23:61; Levy et al., 1985, *Science* 228:190-192; During et al., 1989, *Ann. Neurol.* 25:351-356; Howard et al., 1989, *J. Neurosurg.* 71:858-863). In yet another embodiment, a controlled release system can be placed in proximity of the therapeutic target, i.e., the brain, thus requiring only a fraction of the systemic dose (e.g., Goodson, 1984, In: *Medical Applications of Controlled Release*, *supra*, Vol. 2, pp. 115-138). Other controlled release systems are discussed in the review by Langer (1990, *Science* 249:1527-1533).

In a specific embodiment where the therapeutic is a nucleic acid encoding a protein therapeutic, the nucleic acid can be administered *in vivo* to promote expression of its encoded protein, by constructing it as part of an appropriate nucleic acid expression vector and administering it so that it becomes intracellular, e.g., by use of a retroviral vector (U.S. Patent No. 4,980,286), or by direct injection, or by use of microparticle bombardment (e.g., a gene gun; Biolistic, Dupont), or by coating it with lipids, cell-surface receptors or transfecting agents, or by administering it in linkage to a homeobox-like peptide which is known to enter the nucleus (e.g., Joliot et al., 1991, *Proc. Natl. Acad. Sci. USA* 88:1864-1868), etc. Alternatively, a nucleic acid therapeutic can be introduced

intracellularly and incorporated by homologous recombination within host cell DNA for expression.

The present invention also provides pharmaceutical compositions. Such compositions comprise a therapeutically effective amount of a therapeutic, and a pharmaceutically acceptable carrier. In a specific embodiment, the term "pharmaceutically acceptable" means approved by a regulatory agency of the Federal or a state government or listed in the U.S. Pharmacopeia or other generally recognized pharmacopeia for use in animals, and more particularly, in humans. The term "carrier" refers to a diluent, adjuvant, excipient, or vehicle with which the therapeutic is administered. Such pharmaceutical carriers can be sterile liquids, such as water and oils, including those of petroleum, animal, vegetable or synthetic origin, including but not limited to peanut oil, soybean oil, mineral oil, sesame oil and the like. Water is a preferred carrier when the pharmaceutical composition is administered orally. Saline and aqueous dextrose are preferred carriers when the pharmaceutical composition is administered intravenously. Saline solutions and aqueous dextrose and glycerol solutions are preferably employed as liquid carriers for injectable solutions. Suitable pharmaceutical excipients include starch, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, sodium stearate, glycerol monostearate, talc, sodium chloride, dried skim milk, glycerol, propylene, glycol, water, ethanol and the like. The composition, if desired, can also contain minor amounts of wetting or emulsifying agents, or pH buffering agents. These compositions can take the form of solutions, suspensions, emulsions, tablets, pills, capsules, powders, sustained-release formulations and the like. The composition can be formulated as a suppository, with traditional binders and carriers such as triglycerides. Oral formulation can include standard carriers such as pharmaceutical grades of mannitol, lactose, starch, magnesium stearate, sodium saccharine, cellulose, magnesium carbonate, etc. Examples of suitable pharmaceutical carriers are described in "Remington's Pharmaceutical Sciences" by E.W. Martin. Such compositions will contain a therapeutically effective amount of the therapeutic, preferably in purified form, together with a suitable amount of carrier so as to provide the form for proper administration to the patient. The formulation should suit the mode of administration.

In a preferred embodiment, the composition is formulated, in accordance with routine procedures, as a pharmaceutical composition adapted for intravenous administration to human beings. Typically, compositions for intravenous administration

are solutions in sterile isotonic aqueous buffer. Where necessary, the composition may also include a solubilizing agent and a local anesthetic such as lidocaine to ease pain at the site of the injection. Generally, the ingredients are supplied either separately or mixed together in unit dosage form, for example, as a dry lyophilized powder or water-free concentrate in a hermetically sealed container such as an ampoule or sachette indicating the quantity of active agent. Where the composition is to be administered by infusion, it can be dispensed with an infusion bottle containing sterile pharmaceutical grade water or saline. Where the composition is administered by injection, an ampoule of sterile water or saline for injection can be provided so that the ingredients may be mixed prior to administration.

The therapeutics of the invention can be formulated as neutral or salt forms. Pharmaceutically acceptable salts include those formed with free carboxyl groups such as those derived from hydrochloric, phosphoric, acetic, oxalic, tartaric acids, etc., those formed with free amine groups such as those derived from isopropylamine, triethylamine, 2-ethylamino ethanol, histidine, procaine, etc., and those derived from sodium, potassium, ammonium, calcium, and ferric hydroxides, etc.

The amount of the therapeutic of the invention which will be effective in the treatment of a particular disorder or condition will depend on the nature of the disorder or condition, and can be determined by standard clinical techniques. In addition, in vitro assays may optionally be employed to help identify optimal dosage ranges. The precise dose to be employed in the formulation will also depend on the route of administration, and the seriousness of the disease or disorder, and should be decided according to the judgment of the practitioner and each patient's circumstances. However, suitable dosage ranges for intravenous administration are generally about 20-500 micrograms of active compound per kilogram body weight. Suitable dosage ranges for intranasal administration are generally about 0.01 pg/kg body weight to 1 mg/kg body weight. Effective doses may be extrapolated from dose-response curves derived from in vitro or animal model test systems.

Suppositories generally contain active ingredient in the range of 0.5% to 10% by weight; oral formulations preferably contain 10% to 95% active ingredient.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. Optionally associated with such container(s) can be a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of

pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

The invention also provides a pharmaceutical pack or kit comprising one or more containers filled with one or more of the ingredients of the pharmaceutical compositions of the invention. For example, the kit can comprise in one or more containers a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins listed in the fourth column of table 1; and a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fifth column of table 1.

Alternatively, the kit can comprise in one or more containers, all proteins, functionally active fragments or functionally active derivatives thereof of from the group of proteins in the sixth column of table 1.

The kits of the present invention can also contain expression vectors encoding the essential components of the complex machinery, which components after being expressed can be reconstituted in order to form a biologically active complex. Such a kit preferably also contains the required buffers and reagents. Optionally associated with such container(s) can be instructions for use of the kit and/or a notice in the form prescribed by a governmental agency regulating the manufacture, use or sale of pharmaceuticals or biological products, which notice reflects approval by the agency of manufacture, use or sale for human administration.

#### 4.8 ANIMAL MODELS

The present invention also provides animal models. In one embodiment, animal models for diseases and disorders involving the protein complexes of the present invention are provided. These animal models are well known in the art. These animal models include, but are not limited to those which are listed in the section 4.6 (supra) as exemplary animal models to study any of the complexes provided in the invention. Such animals can be initially produced by promoting homologous recombination or insertional mutagenesis between genes encoding the protein components of the complexes in the chromosome, and exogenous genes encoding the protein components of the complexes that have been rendered biologically inactive or deleted (preferably by insertion of a

heterologous sequence, e.g., an antibiotic resistance gene). In a preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which a gene encoding a component protein from the fourth column of table 1, or a functionally active fragment or functionally active derivative thereof, and a gene encoding a component protein from the fifth column of table 1, or a functionally active fragment or functionally active derivative thereof, has been inactivated or deleted (Capechi, 1989, Science 244:1288-1292).

In another preferred aspect, homologous recombination is carried out by transforming embryo-derived stem (ES) cells with one or more vectors containing one or more insertionally inactivated genes, such that homologous recombination occurs, followed by injecting the transformed ES cells into a blastocyst, and implanting the blastocyst into a foster mother, followed by the birth of the chimeric animal ("knockout animal") in which the genes of all component proteins from the group of proteins listed in the fourth column of table 1 or of all proteins from the group of proteins listed in the fifth column of table 1 have been inactivated or deleted.

The chimeric animal can be bred to produce additional knockout animals. Such animals can be mice, hamsters, sheep, pigs, cattle, etc., and are preferably non-human mammals. In a specific embodiment, a knockout mouse is produced.

Such knockout animals are expected to develop, or be predisposed to developing, diseases or disorders associated with mutations involving the protein complexes of the present invention, and thus, can have use as animal models of such diseases and disorders, e.g., to screen for or test molecules (e.g., potential therapeutics) for such diseases and disorders.

In a different embodiment of the invention, transgenic animals that have incorporated and express (or over-express or mis-express) a functional gene encoding a protein component of the complex, e.g. by introducing the a gene encoding one or more of the components of the complex under the control of a heterologous promoter (i.e., a promoter that is not the native promoter of the gene) that either over-expresses the protein or proteins, or expresses them in tissues not normally expressing the complexes or proteins, can have use as animal models of diseases and disorders characterized by

elevated levels of the protein complexes. Such animals can be used to screen or test molecules for the ability to treat or prevent the diseases and disorders cited supra.

In one embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group of proteins listed in the fourth column of table 1, and an endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins listed in the fifth column of table 1 has been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof. In addition, the present invention provides a recombinant non-human animal in which the endogenous genes of all proteins, or functionally active fragments or functionally active derivatives thereof of one of the group of proteins listed in the sixth column have been deleted or inactivated by homologous recombination or insertional mutagenesis of said animal or an ancestor thereof:

In another embodiment, the present invention provides a recombinant non-human animal in which an endogenous gene encoding a first protein, or a functionally active fragment or functionally active derivative thereof, which first protein is selected from the group consisting of proteins of the fourth column of table 1, and endogenous gene encoding a second protein, or a functionally active fragment or functionally active derivative thereof, which second protein is selected from the group consisting of proteins of the fifth column, of table 1 are recombinantly expressed in said animal or an ancestor thereof.

The following series of examples are presented by way of illustration and not by way of limitation on the scope of the invention.

## EXAMPLES

An object of the present invention was to identify protein complexes of the APP processing pathway, component proteins of the said complexes, fragments and derivatives of the component proteins, and antibodies specific to the complexes. The present invention also relates to methods for use of the complexes of the APP

processing pathway and their interacting proteins in, inter alia, screening, diagnosis, and therapy, as well as to methods of preparing the complexes.

By applying the process according to the invention said complexes were identified. The components are listed in table 1.

APP-C59-complex, Bace1-complex, Bace2-complex, BRI-complex, mDab1-complex, Fe65L2-complex, Plit-complex, Paladin-complex, Neurotrypsin-complex, Hunc18a-complex, Telencephalin-complex, PC7-complex, TFCP2-complex, Jip1-complex, Lamezin-complex, VTRP-complex, p75-NTR-complex

Said object is further achieved by the characterization of component proteins. These proteins are listed in table 2.

Thus, the invention relates to the following embodiments:

The present invention relates to the aph-1a-complex

1. A protein complex selected from complex I and comprising

(a) at least one first protein selected from the group consisting of:

(i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of:
- (i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (ii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (v) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

- (vii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (viii) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,
- (ix) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xi) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xiii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949"

- encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xvi) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xvii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xviii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xix) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xx) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xxiii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxvi) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxvii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxix) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxxi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxxii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1"

encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein aph-1a (SEQ ID No: 1), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'aph-1a' encoded by a nucleic acid that hybridizes to the 'aph-1a' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

- (xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,
- (xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220"

- encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xxix) "SFxn1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFxn1" encoded by a nucleic acid that hybridizes to the "SFxn1" nucleic acid or its complement under low stringency conditions,
- (xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

- (xxxii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxxiii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxxv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxxix) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-32 of the following proteins:

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic

acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

- (xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a

nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

- (xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active

fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 "

- encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,
- (xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

- (xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg"

encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing aph-1a-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a

gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether
  - (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions, and/or

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or

- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1"

encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xxxii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxxix) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated

complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13," encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a

nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22"

encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such

treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

- (iv) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (v) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (vi) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (vii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (viii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (ix) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (x) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xi) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (xii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a

nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xiii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiv) "Endo180" (SEQ ID No: 14) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Endo180" encoded by a nucleic acid that hybridizes to the "Endo180" nucleic acid or its complement under low stringency conditions,

(xv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(xvii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xviii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xix) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(xx) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

- (xxi) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xxii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xxvi) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xxvii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xxix) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1"

encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xxx) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxxi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xxxii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxxiii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxxiv) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxvii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the APP-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
    - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
    - (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
    - (ii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a

nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(iii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(iv) "LAPTM4B" (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B" encoded by a nucleic acid that hybridizes to the "LAPTM4B" nucleic acid or its complement under low stringency conditions,

(v) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(vi) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP (SEQ ID No: 2), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP' encoded by a nucleic acid that hybridizes to the 'APP' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha"

encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-6 of the following proteins:

- (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

- (vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or

functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a

nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.
23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing APP-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether

- (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha"

- encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.
29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or  
(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or  
(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or  
(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid

that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(viii) "LAPTM4B" (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B" encoded by a nucleic acid that hybridizes to the "LAPTM4B" nucleic acid or its complement under low stringency conditions, and/or

(ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and

Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vi) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (vii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (viii) "LAPTM4B" (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B" encoded by a nucleic acid that hybridizes to the "LAPTM4B" nucleic acid or its complement under low stringency conditions,
- (ix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (x) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the APP-C59-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a

nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(ii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(iii) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,

(iv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(v) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(vi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its

complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP-C59 (SEQ ID No: 45), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP-C59' encoded by a nucleic acid that hybridizes to the 'APP-C59' under low stringency conditions.
3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,
- (ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a

nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,

(vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-6 of the following proteins:

(i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a

functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,
- (ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing APP-C59-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether

- (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta"

encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

(i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a

nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or

(vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions, and/or

(vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or

(ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several

interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APP-C59" (SEQ ID No: 45) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C59" encoded by a nucleic acid that hybridizes to the "APP-C59" nucleic acid or its complement under low stringency conditions,
- (ii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (iv) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (v) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

- (vi) "nardilysin" (SEQ ID No: 48) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nardilysin" encoded by a nucleic acid that hybridizes to the "nardilysin" nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (ix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the APP-C99-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a

nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

(iii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(iv) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,

(v) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a

- nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (viii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (ix) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (x) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xv) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two

of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP-C99 (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP-C99' encoded by a nucleic acid that hybridizes to the 'APP-C99' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid

that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,

(ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-15 of the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,

(ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1"

encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
  - (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

- (vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949"

encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing APP-C99-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
  - (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2"

- encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like "

encoded by a nucleic acid that hybridizes to the "Nap1-like" nucleic acid or its complement under low stringency conditions, and/or  
(xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or  
(xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or  
(xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or

several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vi) "Caldesmon" (SEQ ID No: 50) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Caldesmon" encoded by a nucleic acid that hybridizes to the "Caldesmon" nucleic acid or its complement under low stringency conditions,

- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CNIP" (SEQ ID No: 51) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CNIP" encoded by a nucleic acid that hybridizes to the "CNIP" nucleic acid or its complement under low stringency conditions,
- (ix) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (xiii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xiv) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xv) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B "

- encoded by a nucleic acid that hybridizes to the "LAPTM4B" nucleic acid or its complement under low stringency conditions,
- (xvi) "Nap1-like" (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like" encoded by a nucleic acid that hybridizes to the "Nap1-like" nucleic acid or its complement under low stringency conditions,
- (xvii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xviii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xix) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the BACE1-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(iv) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(v) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

- (viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (ix) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (x) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xi) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xiii) "LAPTM4B" (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B" encoded by a nucleic acid that hybridizes to the "LAPTM4B" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,
- (xvi) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a

nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

(xvii) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,

(xviii) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,

(xix) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xx) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xxi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxiv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two

of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein BACE1 (SEQ ID No: 54), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'BACE1' encoded by a nucleic acid that hybridizes to the 'BACE1' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a

nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,

(ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,
- (xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,
- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xxi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,
- (xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2"

- encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-24 of the following proteins:

- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,

(xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xxi) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
  - (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a

nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

(xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,

(xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,

(xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,

(xxi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,

(xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

- (xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing BACE1-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,

protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
  - (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a

- nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a

- nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament

for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

- 37 The method of No. 36 wherein said determining step comprises determining whether
- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
  - (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin"

encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions, and/or

(xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions, and/or

(xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

- (xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "BACE1" (SEQ ID No: 54) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE1" encoded by a nucleic acid that hybridizes to the "BACE1" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (v) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (vi) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (vii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (viii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2"

encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,

(ix) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(x) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(xi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xiii) "GPR49" (SEQ ID No: 52) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GPR49" encoded by a nucleic acid that hybridizes to the "GPR49" nucleic acid or its complement under low stringency conditions,

(xiv) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xv) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(xvi) "LAPTM4B " (SEQ ID No: 42) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "LAPTM4B " encoded by a nucleic acid that hybridizes to the "LAPTM4B " nucleic acid or its complement under low stringency conditions,

- (xvii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xviii) "NogoA" (SEQ ID No: 58) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NogoA" encoded by a nucleic acid that hybridizes to the "NogoA" nucleic acid or its complement under low stringency conditions,
- (xix) "OS-9" (SEQ ID No: 59) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "OS-9" encoded by a nucleic acid that hybridizes to the "OS-9" nucleic acid or its complement under low stringency conditions,
- (xx) "PDGFRB" (SEQ ID No: 60) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PDGFRB" encoded by a nucleic acid that hybridizes to the "PDGFRB" nucleic acid or its complement under low stringency conditions,
- (xi) "PTK7 " (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7 " encoded by a nucleic acid that hybridizes to the "PTK7 " nucleic acid or its complement under low stringency conditions,
- (xxii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xxiv) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the BACE2-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
    - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
    - (ii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid

that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(iii) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vi) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

(x) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xi) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein BACE2 (SEQ ID No: 63), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'BACE2' encoded by a nucleic acid that hybridizes to the 'BACE2' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a

nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

- (xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-12 of the following proteins:

- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 "

- encoded by a nucleic acid that hybridizes to the "calsyntenin 1" nucleic acid or its complement under low stringency conditions,
- (vi) "CGI-13" (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,
- (xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is

attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.

17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
  - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
  - (v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 "

- encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,
- (xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing BACE2-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions, and/or

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament

for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

- 37 The method of No. 36 wherein said determining step comprises determining whether
- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
  - (viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying

the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "BACE2" (SEQ ID No: 63) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BACE2" encoded by a nucleic acid that hybridizes to the "BACE2" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic

acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(v) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

(vi) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(vii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(viii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(ix) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(x) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xi) "ODZ3" (SEQ ID No: 64) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ODZ3" encoded by a nucleic acid that hybridizes to the "ODZ3" nucleic acid or its complement under low stringency conditions,

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

- (xiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the BRI-complex

- 1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(ii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein BRI (SEQ ID No: 8), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'BRI' encoded by a nucleic acid that hybridizes to the 'BRI' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a

nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-2 of the following proteins:

(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said

second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins; or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
  - (iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
  - (v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.
22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing BRI-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition

of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions, and/or
- (v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iv) "CPD" (SEQ ID No: 11) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CPD" encoded by a nucleic acid that hybridizes to the "CPD" nucleic acid or its complement under low stringency conditions,
- (v) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the CtnnB1-complex

1. A protein complex selected from complex (not defined) and comprising

- (a) at least one first protein selected from the group consisting of:
- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
  - (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
  - (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,
  - (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
  - (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
  - (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
  - (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
  - (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein CtnnB1 (SEQ ID No: 65), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'CtnnB1' encoded by a nucleic acid that hybridizes to the 'CtnnB1' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic

acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions,

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-1 of the following proteins:

- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a

- nucleic acid that hybridizes to the "TCF-4" nucleic acid or its complement under low stringency conditions,
- (x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions.
5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
  - (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
  - (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,
  - (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a

nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions,

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing CtnnB1-complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions, and/or
- (x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said

complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic

acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

(viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or

(ix) "TCF-4 " (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4 " encoded by a nucleic acid that hybridizes to the "TCF-4 " nucleic acid or its complement under low stringency conditions, and/or

(x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or

several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "CtnnB1" (SEQ ID No: 65) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "APC" (SEQ ID No: 66) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APC" encoded by a nucleic acid that hybridizes to the "APC" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

- (vii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (viii) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (ix) "TCF-4" (SEQ ID No: 71) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCF-4" encoded by a nucleic acid that hybridizes to the "TCF-4" nucleic acid or its complement under low stringency conditions,
- (x) "ArmVCF" (SEQ ID No: 72) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ArmVCF" encoded by a nucleic acid that hybridizes to the "ArmVCF" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the DAB1-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,
    - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
    - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,

(ii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(iii) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,

(iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta"

- encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (vii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (viii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.
2. The protein complex according to No. 1 wherein the first protein is the protein DAB1 (SEQ ID No: 73), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'DAB1' encoded by a nucleic acid that hybridizes to the 'DAB1' under low stringency conditions.
3. The protein complex according to No. 1 - 2 and comprising the following proteins:
- (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,

- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,
- (viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,
- (x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a

nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-8 of the following proteins:

(i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,
- (viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,
- (ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,
- (x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 "

encoded by a nucleic acid that hybridizes to the "PP2a PR65" nucleic acid or its complement under low stringency conditions,

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by

modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,

(vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,

(viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,

(x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

(xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing DAB1-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
- (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a"

encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions, and/or

(viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions, and/or

(ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions, and/or

(x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or

(xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or

(xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or

(xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated

complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions, and/or
- (x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "DAB1" (SEQ ID No: 73) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB1" encoded by a nucleic acid that hybridizes to the "DAB1" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "DAB2IP" (SEQ ID No: 75) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DAB2IP" encoded by a nucleic acid that hybridizes to the "DAB2IP" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,

(vii) "CK1 delta " (SEQ ID No: 77) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK1 delta " encoded by a nucleic acid that hybridizes to the "CK1 delta " nucleic acid or its complement under low stringency conditions,

(viii) "CRK" (SEQ ID No: 78) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CRK" encoded by a nucleic acid that hybridizes to the "CRK" nucleic acid or its complement under low stringency conditions,

(ix) "FYN" (SEQ ID No: 79) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FYN" encoded by a nucleic acid that hybridizes to the "FYN" nucleic acid or its complement under low stringency conditions,

(x) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,

- (xi) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xiii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Fe65-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
    - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
    - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(ii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(iii) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(iv) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(v) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its

complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Fe65 (SEQ ID No: 83), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Fe65' encoded by a nucleic acid that hybridizes to the 'Fe65' under low stringency conditions.
3. The protein complex according to No. 1 - 2 and comprising the following proteins:
  - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

- acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,
- (xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-5 of the following proteins:

- (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

- (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a

nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a

nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing Fe65-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a

nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions, and/or

(xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.
34. The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.
- 37 The method of No. 36 wherein said determining step comprises determining whether
  - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic

- acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.
38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such

treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.
- 42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins
  - (i) "Fe65" (SEQ ID No: 83) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (ii) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

- (iv) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vii) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (viii) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (ix) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (x) "SAP62" (SEQ ID No: 86) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SAP62" encoded by a nucleic acid that hybridizes to the "SAP62" nucleic acid or its complement under low stringency conditions,
- (xi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Fe65L2-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
    - (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
    - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
    - (ii) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,
    - (iii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a

nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(iv) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,

(v) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

(vi) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,

(vii) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,

(viii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,

(ix) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(x) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,

(xi) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

- (xii) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xiii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (xiv) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xvii) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xviii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55

Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Fe65L2 (SEQ ID No: 87), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Fe65L2' encoded by a nucleic acid that hybridizes to the 'Fe65L2' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
- (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,

- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,
- (x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,
- (xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,
- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a

nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

(xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,

(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-19 of the following proteins:

- (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
- (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,
- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a

nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

(x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,

(xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,

(xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,

(xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,

(xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active

fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,
- (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,
- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a

nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

(x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,

(xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,

(xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,

(xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,

(xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,

(xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,

(xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,

- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,
- (xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing Fe65L2-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,

protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a

- nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions, and/or
- (x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions, and/or

- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15"

- encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and/or  
(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.
29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.
- 37 The method of No. 36 wherein said determining step comprises determining whether
- (i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a

nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions, and/or

(viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions, and/or

(ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions, and/or

(x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions, and/or

(xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions, and/or

(xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2" encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1"

encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "Fe65L2" (SEQ ID No: 87) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L2" encoded by a

nucleic acid that hybridizes to the "Fe65L2" nucleic acid or its complement under low stringency conditions,

(ii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(v) "COPS1" (SEQ ID No: 88) or a functionally active derivative thereof; or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS1" encoded by a nucleic acid that hybridizes to the "COPS1" nucleic acid or its complement under low stringency conditions,

(vi) "COPS2" (SEQ ID No: 89) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS2" encoded by a nucleic acid that hybridizes to the "COPS2" nucleic acid or its complement under low stringency conditions,

(vii) "COPS3" (SEQ ID No: 46) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS3" encoded by a nucleic acid that hybridizes to the "COPS3" nucleic acid or its complement under low stringency conditions,

(viii) "COPS4" (SEQ ID No: 90) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS4" encoded by a nucleic acid that hybridizes to the "COPS4" nucleic acid or its complement under low stringency conditions,

(ix) "COPS5" (SEQ ID No: 91) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS5" encoded by a nucleic acid that hybridizes to the "COPS5" nucleic acid or its complement under low stringency conditions,

- (x) "COPS6" (SEQ ID No: 92) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS6" encoded by a nucleic acid that hybridizes to the "COPS6" nucleic acid or its complement under low stringency conditions,
- (xi) "COPS7b" (SEQ ID No: 93) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS7b" encoded by a nucleic acid that hybridizes to the "COPS7b" nucleic acid or its complement under low stringency conditions,
- (xii) "COPS8" (SEQ ID No: 94) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "COPS8" encoded by a nucleic acid that hybridizes to the "COPS8" nucleic acid or its complement under low stringency conditions,
- (xiii) "Cullin-3" (SEQ ID No: 47) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Cullin-3" encoded by a nucleic acid that hybridizes to the "Cullin-3" nucleic acid or its complement under low stringency conditions,
- (xiv) "Nedd8" (SEQ ID No: 95) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nedd8" encoded by a nucleic acid that hybridizes to the "Nedd8" nucleic acid or its complement under low stringency conditions,
- (xv) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xvi) "RBX1" (SEQ ID No: 96) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RBX1" encoded by a nucleic acid that hybridizes to the "RBX1" nucleic acid or its complement under low stringency conditions,
- (xvii) "RHOBTB1" (SEQ ID No: 97) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB1" encoded by a nucleic acid that hybridizes to the "RHOBTB1" nucleic acid or its complement under low stringency conditions,
- (xviii) "RHOBTB2" (SEQ ID No: 98) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RHOBTB2"

encoded by a nucleic acid that hybridizes to the "RHOBTB2" nucleic acid or its complement under low stringency conditions,

(xix) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xx) "S100beta" (SEQ ID No: 44) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100beta" encoded by a nucleic acid that hybridizes to the "S100beta" nucleic acid or its complement under low stringency conditions,

(xxi) "TNRC15" (SEQ ID No: 99) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TNRC15" encoded by a nucleic acid that hybridizes to the "TNRC15" nucleic acid or its complement under low stringency conditions,

(xxii) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the FKRP-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and
    - (b) at least one first protein selected from the group consisting of:
      - (i) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a

nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(ii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(iii) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(iv) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(v) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(vi) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(vii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(viii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(ix) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

- (x) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xi) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein FKRP (SEQ ID No: 100), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'FKRP' encoded by a nucleic acid that hybridizes to the 'FKRP' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a

- nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

- (x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-13 of the following proteins:

- (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

- encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,
- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.

11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
  - (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
  - (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,

(v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,

(viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

(xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing FKRP-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
- (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a

nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or

(viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or

(xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated

complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.
40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.
- 42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,  
(ii) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a

nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

- (iii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (iv) "EXTL2" (SEQ ID No: 102) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EXTL2" encoded by a nucleic acid that hybridizes to the "EXTL2" nucleic acid or its complement under low stringency conditions,
- (v) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (vi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA0062 Zn transp " (SEQ ID No: 19) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0062 Zn transp " encoded by a nucleic acid that hybridizes to the "KIAA0062 Zn transp " nucleic acid or its complement under low stringency conditions,
- (viii) "KiDins220" (SEQ ID No: 22) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KiDins220" encoded by a nucleic acid that hybridizes to the "KiDins220" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (x) "PP2Cg" (SEQ ID No: 26) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2Cg" encoded by a nucleic acid that hybridizes to the "PP2Cg" nucleic acid or its complement under low stringency conditions,

- (xi) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xii) "TLOC1" (SEQ ID No: 104) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TLOC1" encoded by a nucleic acid that hybridizes to the "TLOC1" nucleic acid or its complement under low stringency conditions,
- (xiii) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the GSK3a-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
    - (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,
    - (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a

nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,

(ii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,

(iii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,

(iv) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,

(v) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,

(vi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1"

encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,

(vii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(viii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,

(ix) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,

(x) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,

(xi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,

(xii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xiii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xiv) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two

of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein GSK3a (SEQ ID No: 106), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'GSK3a' encoded by a nucleic acid that hybridizes to the 'GSK3a' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,
- (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,
- (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,
- (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a

nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,
- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,

- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-14 of the following proteins:

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic

acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,

(iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,

(iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,

(v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

(vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,

(vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,

(viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,

(ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,

(x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,

- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune "

encoded by a nucleic acid that hybridizes to the "TcD37/prune" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.

10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.

18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
  - (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,
  - (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,
  - (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,
  - (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,

- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,
- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta"

- encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,
- (xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing GSK3a-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28. The method of No. 27 wherein said determining step comprises determining whether

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like "

- encoded by a nucleic acid that hybridizes to the "Nap1-like" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PKA reg I alpha" (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha" encoded by a nucleic acid that hybridizes to the "PKA reg I alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "PP2a PR65" (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65" encoded by a nucleic acid that hybridizes to the "PP2a PR65" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "TcD37/prune" (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune" encoded by a nucleic acid that hybridizes to the "TcD37/prune" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions, and/or

- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions, and/or
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions, and/or
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56

gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions, and/or  
(xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or  
(xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and/or  
(xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or

several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "GSK3a" (SEQ ID No: 106) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "GSK3a" encoded by a nucleic acid that hybridizes to the "GSK3a" nucleic acid or its complement under low stringency conditions,
- (ii) "Axin" (SEQ ID No: 107) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Axin" encoded by a nucleic acid that hybridizes to the "Axin" nucleic acid or its complement under low stringency conditions,
- (iii) "FRAT1" (SEQ ID No: 108) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT1" encoded by a nucleic acid that hybridizes to the "FRAT1" nucleic acid or its complement under low stringency conditions,
- (iv) "FRAT2" (SEQ ID No: 109) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FRAT2" encoded by a nucleic acid that hybridizes to the "FRAT2" nucleic acid or its complement under low stringency conditions,
- (v) "rAxin1" (SEQ ID No: 110) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "rAxin1" encoded by a nucleic acid that hybridizes to the "rAxin1" nucleic acid or its complement under low stringency conditions,
- (vi) "AKAP11" (SEQ ID No: 111) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "AKAP11" encoded by a nucleic acid that hybridizes to the "AKAP11" nucleic acid or its complement under low stringency conditions,

- (vii) "C14orf129 (DUF727)" (SEQ ID No: 112) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "C14orf129 (DUF727)" encoded by a nucleic acid that hybridizes to the "C14orf129 (DUF727)" nucleic acid or its complement under low stringency conditions,
- (viii) "calcineurin A alpha " (SEQ ID No: 113) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A alpha " encoded by a nucleic acid that hybridizes to the "calcineurin A alpha " nucleic acid or its complement under low stringency conditions,
- (ix) "calcineurin A beta" (SEQ ID No: 114) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calcineurin A beta" encoded by a nucleic acid that hybridizes to the "calcineurin A beta" nucleic acid or its complement under low stringency conditions,
- (x) "cdc37" (SEQ ID No: 115) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "cdc37" encoded by a nucleic acid that hybridizes to the "cdc37" nucleic acid or its complement under low stringency conditions,
- (xi) "DSCR1" (SEQ ID No: 116) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCR1" encoded by a nucleic acid that hybridizes to the "DSCR1" nucleic acid or its complement under low stringency conditions,
- (xii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (xiii) "PKA cat alpha" (SEQ ID No: 117) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat alpha" encoded by a nucleic acid that hybridizes to the "PKA cat alpha" nucleic acid or its complement under low stringency conditions,
- (xiv) "PKA cat beta" (SEQ ID No: 118) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA cat beta" encoded by a nucleic acid that hybridizes to the "PKA cat beta" nucleic acid or its complement under low stringency conditions,
- (xv) "PKA reg I alpha " (SEQ ID No: 119) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PKA reg I

alpha " encoded by a nucleic acid that hybridizes to the "PKA reg I alpha " nucleic acid or its complement under low stringency conditions,

(xvi) "PP2a B56 gamma" (SEQ ID No: 120) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a B56 gamma" encoded by a nucleic acid that hybridizes to the "PP2a B56 gamma" nucleic acid or its complement under low stringency conditions,

(xvii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(xviii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions,

(xix) "TcD37/prune " (SEQ ID No: 121) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TcD37/prune " encoded by a nucleic acid that hybridizes to the "TcD37/prune " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the JIP1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,

(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,

- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,
  - (iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of: and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein JIP1 (SEQ ID No: 122), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'JIP1' encoded by a nucleic acid that hybridizes to the 'JIP1' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,
- (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,
- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a

nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-0 of the following proteins:

(i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,

(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,

(iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,
- (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,
- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,
- (iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing JIP1-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
  - (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions, and/or

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether  
(i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions, and/or  
(iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions, and/or  
(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "JIP1" (SEQ ID No: 122) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JIP1" encoded by a nucleic acid that hybridizes to the "JIP1" nucleic acid or its complement under low stringency conditions,
- (ii) "KLC1" (SEQ ID No: 123) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KLC1" encoded by a nucleic acid that hybridizes to the "KLC1" nucleic acid or its complement under low stringency conditions,
- (iii) "nKHC2" (SEQ ID No: 124) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "nKHC2" encoded by a

nucleic acid that hybridizes to the "nKHC2" nucleic acid or its complement under low stringency conditions,

(iv) "uKHC" (SEQ ID No: 125) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "uKHC" encoded by a nucleic acid that hybridizes to the "uKHC" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Nicastrin-complex

1. A protein complex selected from complex (not defined) and comprising,
  - (a) at least one first protein selected from the group consisting of:
    - (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
    - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
    - (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
    - (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
    - (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
  - (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
  - (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
  - (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
  - (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
  - (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and
- (b) at least one first protein selected from the group consisting of:
- (i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
  - (ii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

- (iii) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,
- (iv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (v) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vi) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (vii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (viii) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (ix) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (x) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363"

- encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiii) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xiv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xv) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

- (xx) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxi) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxiv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xxv) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,
- (xxvi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxvii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA,

0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein APP-C99 (SEQ ID No: 3), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'APP-C99' encoded by a nucleic acid that hybridizes to the 'APP-C99' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a

nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,

(xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2"

- encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-27 of the following proteins:

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a

nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

(xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,

(xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

- (xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2"

- encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

- (xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,
- (xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the

expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or

functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
  - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,

(vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,
- (xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,
- (xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481"

- encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,
- (xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1"

encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing Nicastin-complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether

(i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or

- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a

- nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or  
(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or  
(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or  
(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or  
(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and/or  
(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or  
(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament

for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

- 37 The method of No. 36 wherein said determining step comprises determining whether
- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or
  - (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3"

encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions, and/or

- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or
- (xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or
- (xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21"

encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions, and/or

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several

interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (ii) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions,
- (iii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iv) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (v) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

- (vi) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (viii) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (ix) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (x) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (xi) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (xii) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (xiii) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (xiv) "CK2B" (SEQ ID No: 127) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CK2B" encoded by a

nucleic acid that hybridizes to the "CK2B" nucleic acid or its complement under low stringency conditions,

(xv) "CLGN" (SEQ ID No: 101) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CLGN" encoded by a nucleic acid that hybridizes to the "CLGN" nucleic acid or its complement under low stringency conditions,

(xvi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(xvii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,

(xviii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,

(xix) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xx) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(xxi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(xxii) "KIAA0363" (SEQ ID No: 20) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0363" encoded by a nucleic acid that hybridizes to the "KIAA0363" nucleic acid or its complement under low stringency conditions,

- (xxiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xxv) "PTP LOC114971" (SEQ ID No: 130) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTP LOC114971" encoded by a nucleic acid that hybridizes to the "PTP LOC114971" nucleic acid or its complement under low stringency conditions,
- (xxvi) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xxvii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xxviii) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xxix) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxx) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxxi) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2"

encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxxii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxxv) "UGCGL1" (SEQ ID No: 62) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "UGCGL1" encoded by a nucleic acid that hybridizes to the "UGCGL1" nucleic acid or its complement under low stringency conditions,

(xxxvi) "visinin-like 1" (SEQ ID No: 49) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "visinin-like 1" encoded by a nucleic acid that hybridizes to the "visinin-like 1" nucleic acid or its complement under low stringency conditions,

(xxxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the pen-2-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
    - (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
    - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
    - (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
    - (ii) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
    - (iii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

- (iv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (v) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (vi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (vii) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (viii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (ix) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (x) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xi) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a

nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xiii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xiv) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xvi) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein pen-2 (SEQ ID No: 132), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'pen-2' encoded by a nucleic acid that hybridizes to the 'pen-2' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,
- (viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a

nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

(xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,

(xvi) "SFN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFN1" encoded by a nucleic acid that hybridizes to the "SFN1" nucleic acid or its complement under low stringency conditions,

- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-17 of the following proteins:

- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,

(iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a

nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.
6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
  - (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a

nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,

(xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,

- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin"

encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing pen-2-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.

25. The method of No. 23 wherein the activity of said complex is determined.

26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

- 28 The method of No. 27 wherein said determining step comprises determining whether
- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or
  - (vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or
  - (vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions, and/or
  - (viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22"

encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or

(xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37. The method of No. 36 wherein said determining step comprises determining whether  
(i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a

nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or

(vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions, and/or

(viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

- (xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a

nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (ii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (v) "ACAT1" (SEQ ID No: 7) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ACAT1" encoded by a nucleic acid that hybridizes to the "ACAT1" nucleic acid or its complement under low stringency conditions,
- (vi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (vii) "copine III" (SEQ ID No: 134) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "copine III" encoded by a nucleic acid that hybridizes to the "copine III" nucleic acid or its complement under low stringency conditions,

- (viii) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "KIAA1102" (SEQ ID No: 135) or a functionally active derivative thereof; or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1102" encoded by a nucleic acid that hybridizes to the "KIAA1102" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA1949" (SEQ ID No: 21) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA1949" encoded by a nucleic acid that hybridizes to the "KIAA1949" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (xv) "S100alpha" (SEQ ID No: 43) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "S100alpha" encoded by a nucleic acid that hybridizes to the "S100alpha" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a

nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xix) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xx) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xi) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Psen1-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions,

- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a

nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and

- (b) at least one first protein selected from the group consisting of:
  - (i) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
  - (ii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
  - (iii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
  - (iv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
  - (v) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
  - (vi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
  - (vii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
  - (viii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a

nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(ix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(x) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two

of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Nicastrin (SEQ ID No: 5), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Nicastrin' encoded by a nucleic acid that hybridizes to the 'Nicastrin' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a

nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

(vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,

(vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,

(viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

(ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,

(x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,

(xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,

(xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,

(xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25"

encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-16 of the following proteins:

- (i) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75"

- encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a

functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
  - (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
  - (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
  - (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,
  - (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
  - (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
  - (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,

- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090"

- encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

- (xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.
22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.
23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing Psen1-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.

27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.

28 The method of No. 27 wherein said determining step comprises determining whether  
(i) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions, and/or

(ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or

(iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or

(v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic

acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

(ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or

(x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or

(xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or

(xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or

(xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD"

encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.
- 37 The method of No. 36 wherein said determining step comprises determining whether
- (i) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions, and/or
  - (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a

nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions, and/or

(vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions, and/or

(vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions, and/or

(viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions, and/or

(ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions, and/or

(x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions, and/or

(xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions, and/or

(xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25"

encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or

(xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or

(xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or

(xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or

(xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several

interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (ii) "Psen1" (SEQ ID No: 6) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen1" encoded by a nucleic acid that hybridizes to the "Psen1" nucleic acid or its complement under low stringency conditions,
- (iii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iv) "CtnnA1" (SEQ ID No: 67) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA1" encoded by a nucleic acid that hybridizes to the "CtnnA1" nucleic acid or its complement under low stringency conditions,
- (v) "CtnnA2" (SEQ ID No: 68) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnA2" encoded by a nucleic acid that hybridizes to the "CtnnA2" nucleic acid or its complement under low stringency conditions,

- (vi) "CtnnB1" (SEQ ID No: 126) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnB1" encoded by a nucleic acid that hybridizes to the "CtnnB1" nucleic acid or its complement under low stringency conditions,
- (vii) "CtnnD1" (SEQ ID No: 69) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CtnnD1" encoded by a nucleic acid that hybridizes to the "CtnnD1" nucleic acid or its complement under low stringency conditions,
- (viii) "JUP" (SEQ ID No: 4) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "JUP" encoded by a nucleic acid that hybridizes to the "JUP" nucleic acid or its complement under low stringency conditions,
- (ix) "NCadh" (SEQ ID No: 70) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NCadh" encoded by a nucleic acid that hybridizes to the "NCadh" nucleic acid or its complement under low stringency conditions,
- (x) "pen-2" (SEQ ID No: 132) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "pen-2" encoded by a nucleic acid that hybridizes to the "pen-2" nucleic acid or its complement under low stringency conditions,
- (xi) "CaMKIIa" (SEQ ID No: 133) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CaMKIIa" encoded by a nucleic acid that hybridizes to the "CaMKIIa" nucleic acid or its complement under low stringency conditions,
- (xii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (xiii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (xiv) "FKRP" (SEQ ID No: 100) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FKRP" encoded by a

nucleic acid that hybridizes to the "FKRP" nucleic acid or its complement under low stringency conditions,

(xv) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

(xvi) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,

(xvii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xix) "SARM" (SEQ ID No: 28) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SARM" encoded by a nucleic acid that hybridizes to the "SARM" nucleic acid or its complement under low stringency conditions,

(xx) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xi) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

- (xxiii) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxiv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxv) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvi) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the Psen2-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,
    - (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
    - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a

nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and

- (b) at least one first protein selected from the group consisting of:
  - (i) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
  - (ii) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
  - (iii) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
  - (iv) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
  - (v) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
  - (vi) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
  - (vii) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
  - (viii) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a

nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,

(ix) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

(x) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,

(xi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,

(xii) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,

(xiii) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,

(xiv) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,

(xv) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xvi) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

- (xvii) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xviii) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xix) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xx) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxi) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxii) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxiii) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxiv) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxv) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1"

encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC; 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein Psen2 (SEQ ID No: 304), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'Psen2' encoded by a nucleic acid that hybridizes to the 'Psen2' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,
- (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,

- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a

- nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvii) "Wolfamin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolfamin" encoded by a nucleic acid that hybridizes to the "Wolfamin" nucleic acid or its complement under low stringency conditions,
- (xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-25 of the following proteins:

- (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a

- nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,
- (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions,
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,

- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1"

encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,

(xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,

(xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

(xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,
  - (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,
  - (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions,
  - (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 "

- encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,

- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,
- (xi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25"

encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,

(xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,

(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,

(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,

(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,

(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,

(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,

(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing Psen2-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481"

- encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or

- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or
- (xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or
- (xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or
- (xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or
- (xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or
- (xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin"

- encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or  
(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.
29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

(i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions, and/or

(ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions, and/or

(iii) "Nicastrin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastrin" encoded by a nucleic acid that hybridizes to the "Nicastrin" nucleic acid or its complement under low stringency conditions, and/or

(iv) "CGI-13 " (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13 " encoded by a nucleic acid that hybridizes to the "CGI-13 " nucleic acid or its complement under low stringency conditions, and/or

(v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a

nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions, and/or

(vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions, and/or

(viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions, and/or

(x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions, and/or

(xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions, and/or

(xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090" encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions, and/or

- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, and/or
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions, and/or
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions, and/or
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions, and/or
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions, and/or
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions, and/or
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions, and/or
- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions, and/or
- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2"

encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions, and/or  
(xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions, and/or  
(xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions, and/or  
(xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions, and/or  
(xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions, and/or  
(xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions, and/or  
(xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such

treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "Psen2" (SEQ ID No: 304) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Psen2" encoded by a nucleic acid that hybridizes to the "Psen2" nucleic acid or its complement under low stringency conditions,

(ii) "aph-1a" (SEQ ID No: 1) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "aph-1a" encoded by a nucleic acid that hybridizes to the "aph-1a" nucleic acid or its complement under low stringency conditions,

(iii) "Nicastin" (SEQ ID No: 5) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nicastin" encoded by a nucleic acid that hybridizes to the "Nicastin" nucleic acid or its complement under low stringency conditions,

- (iv) "CGI-13" (SEQ ID No: 10) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CGI-13" encoded by a nucleic acid that hybridizes to the "CGI-13" nucleic acid or its complement under low stringency conditions,
- (v) "DSCD75" (SEQ ID No: 13) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DSCD75" encoded by a nucleic acid that hybridizes to the "DSCD75" nucleic acid or its complement under low stringency conditions,
- (vi) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (vii) "FACL3" (SEQ ID No: 15) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FACL3" encoded by a nucleic acid that hybridizes to the "FACL3" nucleic acid or its complement under low stringency conditions,
- (viii) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (ix) "FLJ10579" (SEQ ID No: 16) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ10579" encoded by a nucleic acid that hybridizes to the "FLJ10579" nucleic acid or its complement under low stringency conditions,
- (x) "FLJ20481" (SEQ ID No: 129) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FLJ20481" encoded by a nucleic acid that hybridizes to the "FLJ20481" nucleic acid or its complement under low stringency conditions,
- (xi) "ITPR1" (SEQ ID No: 18) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITPR1" encoded by a nucleic acid that hybridizes to the "ITPR1" nucleic acid or its complement under low stringency conditions,
- (xii) "KIAA0090" (SEQ ID No: 136) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "KIAA0090"

- encoded by a nucleic acid that hybridizes to the "KIAA0090" nucleic acid or its complement under low stringency conditions,
- (xviii) "MDR1" (SEQ ID No: 23) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "MDR1" encoded by a nucleic acid that hybridizes to the "MDR1" nucleic acid or its complement under low stringency conditions,
- (xiv) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions,
- (xv) "PLD3" (SEQ ID No: 25) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PLD3" encoded by a nucleic acid that hybridizes to the "PLD3" nucleic acid or its complement under low stringency conditions,
- (xvi) "SFXN1" (SEQ ID No: 29) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SFXN1" encoded by a nucleic acid that hybridizes to the "SFXN1" nucleic acid or its complement under low stringency conditions,
- (xvii) "SLC4A2" (SEQ ID No: 321) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SLC4A2" encoded by a nucleic acid that hybridizes to the "SLC4A2" nucleic acid or its complement under low stringency conditions,
- (xviii) "SORT1" (SEQ ID No: 137) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORT1" encoded by a nucleic acid that hybridizes to the "SORT1" nucleic acid or its complement under low stringency conditions,
- (xix) "SPC18" (SEQ ID No: 31) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC18" encoded by a nucleic acid that hybridizes to the "SPC18" nucleic acid or its complement under low stringency conditions,
- (xx) "SPC22" (SEQ ID No: 32) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC22" encoded by a nucleic acid that hybridizes to the "SPC22" nucleic acid or its complement under low stringency conditions,

- (xxi) "SPC25" (SEQ ID No: 33) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPC25" encoded by a nucleic acid that hybridizes to the "SPC25" nucleic acid or its complement under low stringency conditions,
- (xxii) "SPTLC2" (SEQ ID No: 34) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPTLC2" encoded by a nucleic acid that hybridizes to the "SPTLC2" nucleic acid or its complement under low stringency conditions,
- (xxiii) "stearoyl-CoA desaturase" (SEQ ID No: 35) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "stearoyl-CoA desaturase" encoded by a nucleic acid that hybridizes to the "stearoyl-CoA desaturase" nucleic acid or its complement under low stringency conditions,
- (xxiv) "STT3" (SEQ ID No: 131) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "STT3" encoded by a nucleic acid that hybridizes to the "STT3" nucleic acid or its complement under low stringency conditions,
- (xxv) "TMP21" (SEQ ID No: 36) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TMP21" encoded by a nucleic acid that hybridizes to the "TMP21" nucleic acid or its complement under low stringency conditions,
- (xxvi) "VLCAD" (SEQ ID No: 37) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "VLCAD" encoded by a nucleic acid that hybridizes to the "VLCAD" nucleic acid or its complement under low stringency conditions,
- (xxvii) "Wolframin" (SEQ ID No: 105) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Wolframin" encoded by a nucleic acid that hybridizes to the "Wolframin" nucleic acid or its complement under low stringency conditions,
- (xxviii) "YME1L1" (SEQ ID No: 38) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "YME1L1" encoded by a nucleic acid that hybridizes to the "YME1L1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the PTK7-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
    - (ii) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
    - (iii) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
    - (iv) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
    - (v) "HIFPH3/EGLN3" (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of

"HIFPH3/EGLN3" encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3" nucleic acid or its complement under low stringency conditions,

(vi) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(vii) "Nap1-like" (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like" encoded by a nucleic acid that hybridizes to the "Nap1-like" nucleic acid or its complement under low stringency conditions,

(viii) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein PTK7 (SEQ ID No: 61), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'PTK7' encoded by a nucleic acid that hybridizes to the 'PTK7' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

(i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,

- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a

nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-8 of the following proteins:

- (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,

- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA)

and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).

15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
  - (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic

- acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing PTK7-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions, and/or
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a

nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions, and/or
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a

nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions, and/or

(vii) "HIFPH3/EGLN3 " (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3 " encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3 " nucleic acid or its complement under low stringency conditions, and/or

(viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or

(ix) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several

interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "PTK7" (SEQ ID No: 61) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PTK7" encoded by a nucleic acid that hybridizes to the "PTK7" nucleic acid or its complement under low stringency conditions,
- (ii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iii) "BRI" (SEQ ID No: 8) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BRI" encoded by a nucleic acid that hybridizes to the "BRI" nucleic acid or its complement under low stringency conditions,
- (iv) "CELSR2" (SEQ ID No: 56) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "CELSR2" encoded by a nucleic acid that hybridizes to the "CELSR2" nucleic acid or its complement under low stringency conditions,
- (v) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

- (vi) "FADS2" (SEQ ID No: 57) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "FADS2" encoded by a nucleic acid that hybridizes to the "FADS2" nucleic acid or its complement under low stringency conditions,
- (vii) "HIFPH3/EGLN3" (SEQ ID No: 339) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HIFPH3/EGLN3" encoded by a nucleic acid that hybridizes to the "HIFPH3/EGLN3" nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 103) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Nap1-like" (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like" encoded by a nucleic acid that hybridizes to the "Nap1-like" nucleic acid or its complement under low stringency conditions,
- (x) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the SPPL3-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
    - (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a

nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and

(b) at least one first protein selected from the group consisting of:

(i) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(ii) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(iii) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein SPPL3 (SEQ ID No: 343), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'SPPL3' encoded by a nucleic acid that hybridizes to the 'SPPL3' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-3 of the following proteins:

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a

nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in

cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).

14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,

- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing SPPL3-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity,

protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
28. The method of No. 27 wherein said determining step comprises determining whether
  - (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
  - (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a

nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity,

or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34 The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a

nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions, and/or

(v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions, and/or

(vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "SPPL3" (SEQ ID No: 343) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SPPL3" encoded by a nucleic acid that hybridizes to the "SPPL3" nucleic acid or its complement under low stringency conditions,
- (ii) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (iii) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (iv) "ECSIT" (SEQ ID No: 128) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ECSIT" encoded by a nucleic acid that hybridizes to the "ECSIT" nucleic acid or its complement under low stringency conditions,
- (v) "Nap1-like " (SEQ ID No: 53) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Nap1-like " encoded by a nucleic acid that hybridizes to the "Nap1-like " nucleic acid or its complement under low stringency conditions,
- (vi) "NicAChRa3" (SEQ ID No: 318) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "NicAChRa3" encoded by a nucleic acid that hybridizes to the "NicAChRa3" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the tau-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
    - (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
    - (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
    - (ii) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
    - (iii) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55

Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein tau (SEQ ID No: 349), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'tau' encoded by a nucleic acid that hybridizes to the 'tau' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-3 of the following proteins:

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.

13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.

21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing tau-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37. The method of No. 36 wherein said determining step comprises determining whether (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions, and/or
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta" encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the

interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

- (i) "tau" (SEQ ID No: 349) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "tau" encoded by a nucleic acid that hybridizes to the "tau" nucleic acid or its complement under low stringency conditions,
- (ii) "14-3-3 zeta" (SEQ ID No: 350) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "14-3-3 zeta" encoded by a nucleic acid that hybridizes to the "14-3-3 zeta" nucleic acid or its complement under low stringency conditions,
- (iii) "PP2a PR55a" (SEQ ID No: 76) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR55a" encoded by a nucleic acid that hybridizes to the "PP2a PR55a" nucleic acid or its complement under low stringency conditions,
- (iv) "HSP105" (SEQ ID No: 80) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "HSP105" encoded by a nucleic acid that hybridizes to the "HSP105" nucleic acid or its complement under low stringency conditions,
- (v) "PP2a cat beta" (SEQ ID No: 81) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a cat beta"

encoded by a nucleic acid that hybridizes to the "PP2a cat beta" nucleic acid or its complement under low stringency conditions,

(vi) "PP2a PR65 " (SEQ ID No: 82) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "PP2a PR65 " encoded by a nucleic acid that hybridizes to the "PP2a PR65 " nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the TIP60-complex

1. A protein complex selected from complex (not defined) and comprising

(a) at least one first protein selected from the group consisting of:

(i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions, and

- (b) at least one first protein selected from the group consisting of:
- (i) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
  - (ii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,
  - (iii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,
  - (iv) "TCFL1/YL1" (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1" encoded by a nucleic acid that hybridizes to the "TCFL1/YL1" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein TIP60 (SEQ ID No: 84), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'TIP60' encoded by a nucleic acid that hybridizes to the 'TIP60' under low stringency conditions.

3. The protein complex according to No. 1 - 2 and comprising the following proteins:

- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a

nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-4 of the following proteins:

- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
- (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,
- (v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,
- (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,
- (vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,
- (viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400"

encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.

7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.

8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).

9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.

16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.
20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
  - (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,
  - (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,
  - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,
  - (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a

nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TTRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TTRAP" encoded by a nucleic acid that hybridizes to the "TTRAP" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 " encoded by a nucleic acid that hybridizes to the "TCFL1/YL1 " nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing TIP60-complex to one or more candidate molecules; and

(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the

presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.

24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether
  - (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
  - (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions, and/or
  - (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or

- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "TCFL1/YL1" (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1" encoded by a nucleic acid that hybridizes to the "TCFL1/YL1" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.
32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.
33. The method of No. 32 wherein the amount of said complex is determined.
- 34 The method of No. 32 wherein the activity of said complex is determined.
35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.
- 37 The method of No. 36 wherein said determining step comprises determining whether

- (i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions, and/or
- (ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions, and/or
- (v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions, and/or
- (vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "TCFL1/YL1 " (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1 "

encoded by a nucleic acid that hybridizes to the "TCFL1/YL1" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins  
(i) "TIP60" (SEQ ID No: 84) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TIP60" encoded by a

nucleic acid that hybridizes to the "TIP60" nucleic acid or its complement under low stringency conditions,

(ii) "BAF53" (SEQ ID No: 356) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "BAF53" encoded by a nucleic acid that hybridizes to the "BAF53" nucleic acid or its complement under low stringency conditions,

(iii) "Fe65" (SEQ ID No: 39) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65" encoded by a nucleic acid that hybridizes to the "Fe65" nucleic acid or its complement under low stringency conditions,

(iv) "Fe65L1" (SEQ ID No: 40) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Fe65L1" encoded by a nucleic acid that hybridizes to the "Fe65L1" nucleic acid or its complement under low stringency conditions,

(v) "TRRAP" (SEQ ID No: 359) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TRRAP" encoded by a nucleic acid that hybridizes to the "TRRAP" nucleic acid or its complement under low stringency conditions,

(vi) "DLK1" (SEQ ID No: 12) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DLK1" encoded by a nucleic acid that hybridizes to the "DLK1" nucleic acid or its complement under low stringency conditions,

(vii) "DMAP1" (SEQ ID No: 361) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "DMAP1" encoded by a nucleic acid that hybridizes to the "DMAP1" nucleic acid or its complement under low stringency conditions,

(viii) "EP400" (SEQ ID No: 362) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "EP400" encoded by a nucleic acid that hybridizes to the "EP400" nucleic acid or its complement under low stringency conditions,

(ix) "TCFL1/YL1" (SEQ ID No: 363) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TCFL1/YL1" encoded by a nucleic acid that hybridizes to the "TCFL1/YL1" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a

pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

Furthermore, the present invention relates to the X11beta-complex

1. A protein complex selected from complex (not defined) and comprising
  - (a) at least one first protein selected from the group consisting of:
    - (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
    - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
    - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
    - (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
    - (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and
  - (b) at least one first protein selected from the group consisting of:
    - (i) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,

- (ii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (iii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (iv) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (v) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (vi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (vii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (viii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (ix) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, and a complex (II) comprising at least two of said second proteins, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll,

0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40 Celsius, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 55 Celsius, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60 Celsius.

2. The protein complex according to No. 1 wherein the first protein is the protein X11beta (SEQ ID No: 364), or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of 'X11beta' encoded by a nucleic acid that hybridizes to the 'X11beta' under low stringency conditions.
3. The protein complex according to No. 1 - 2 and comprising the following proteins:
  - (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a

nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions.

4. The protein complex according to No. 1 comprising all but 1-9 of the following proteins:

- (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions.

5. The complex of any of No. 1 - 4 comprising a functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an amino acid sequence different from the first protein or second protein, respectively.

6. The complex of No. 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of No. 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of No. 1 - 7 that is involved in the transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)).
9. A process for preparing a complex of any of No. 1 - 8 and optionally the components thereof comprising the following steps: expressing a protein (bait) of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the bait protein, and optionally dissociating the protein complex and isolating the individual complex members.
10. The process according to No. 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of No. 9 - 10 wherein the two tags are separated by a cleavage site for a protease.

12. Component of the Fe65 complex obtainable by a process according to any of No. 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative of at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the first group of proteins according to No. 1 (a) and at least one of said proteins, or functionally active fragments or functionally active derivative thereof being selected from the second group of proteins according to No. 1 (b).
14. Host cell, containing a construct of No. 13 or containing several vectors each comprising at least the nucleic acid sequence encoding at least one of the proteins, or functionally active fragments or functionally active derivatives thereof selected from the first group of proteins according to No. 1 (a) and the proteins, or functionally active fragments or functionally active derivatives thereof selected from the second group of proteins according to No. 1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, selected from an antibody or fragment thereof, which binds the complex of any of No. 1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more container the complex of any of No. 1 - 8 optionally together with an antibody according to No. 15 and/or further components such as reagents and working instructions.
17. The kit according to No. 16 for processing a substrate of said complex.
18. The kit according to No. 16 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.
19. Array, in which at least a complex according to any of No. 1 - 8 and/or at least one antibody according to No. 15 is attached to a solid carrier.

20. A process for processing a physiological substrate of the complex comprising the step of bringing into contact a complex to any of No. 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of No. 1 - 8 and/or any of the following the proteins:
- (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,
  - (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,
  - (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,
  - (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,
  - (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,
  - (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions,
  - (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2"

- encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,
- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,
- (xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,
- (xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,
- (xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,
- (xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions.,and a pharmaceutical acceptable carrier.

22. A pharmaceutical composition according to No. 21 for the treatment of diseases and disorders such as neurodegenerative disease such as Alzheimer's disease.

23. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of No. 1 - 8 comprising the steps of:(a) exposing said complex, or a cell or organism containing X11beta-complex to one or more candidate molecules; and  
(b) determining the amount of activity of protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity or composition of said complex.
24. The method of No. 23, wherein the amount of said complex is determined.
25. The method of No. 23 wherein the activity of said complex is determined.
26. The method of No. 25 wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining the processing of said substrate is modified in the presence of said candidate molecule.
27. The method of No. 24 wherein the amount of the individual protein components of said complex are determined.
- 28 The method of No. 27 wherein said determining step comprises determining whether (i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or

- (ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a

nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

(xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or

(xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or

(xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or

(xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4," encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, is present in the complex.

29. The method of any of No. 23- 28 wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

30. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of No. 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

31. A method for the production of a pharmaceutical composition comprising carrying out the method of any of No. 1 - 8 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

32. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, activity of, or component composition of, or intracellular localization of the complex of any one of the No. 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicates the presence in the subject of the disease or disorder or predisposition in the subject.

33. The method of No. 32 wherein the amount of said complex is determined.

34. The method of No. 32 wherein the activity of said complex is determined.

35. The method of No. 34 wherein said determining step comprises isolating from the subject said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

36. The method of No. 32 wherein the amount of the individual protein components of said complex is determined.

37. The method of No. 36 wherein said determining step comprises determining whether  
(i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions, and/or  
(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a

- nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions, and/or
- (iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions, and/or
- (iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions, and/or
- (v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions, and/or
- (vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 " encoded by a nucleic acid that hybridizes to the "calsyntenin 1 " nucleic acid or its complement under low stringency conditions, and/or
- (vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions, and/or
- (viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions, and/or
- (ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions, and/or
- (x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions, and/or

- (xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions, and/or
- (xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions, and/or
- (xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions, and/or
- (xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, is present in the complex.

38. The complex of any one of No. 1 - 8, or the antibody or fragment of No. 15, for use in a method of diagnosing a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity or component composition of or intracellular localization of, the complex of anyone of No. 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, transactivation of a Gal4-driven reporter gene (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of Abeta-40 and Abeta-42 peptides by ELISA (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), the production of C-terminal APP fragments in cell lines or transgenic animals by western blot (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)) or the proteolytic activity of beta- or gamma secretases towards

bacterially expressed APP fragments in vitro (e.g. by modifying the expression of one or several interacting proteins in cells by means of RNAi (siRNA) and/or plasmids encoding the interacting protein(s)), or protein components of, said complex.

40. The method according to No. 39 wherein said disease or disorder involves decreased levels of the amount or activity of said complex.

41. The method according to No. 39 wherein said disease or disorder involves increased levels of the amount or activity of said complex.

42 Complex of any of No. 1 - 8 and/or protein selected from the following proteins

(i) "X11beta" (SEQ ID No: 364) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "X11beta" encoded by a nucleic acid that hybridizes to the "X11beta" nucleic acid or its complement under low stringency conditions,

(ii) "APLP1" (SEQ ID No: 74) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP1" encoded by a nucleic acid that hybridizes to the "APLP1" nucleic acid or its complement under low stringency conditions,

(iii) "APLP2" (SEQ ID No: 55) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APLP2" encoded by a nucleic acid that hybridizes to the "APLP2" nucleic acid or its complement under low stringency conditions,

(iv) "APP" (SEQ ID No: 2) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP" encoded by a nucleic acid that hybridizes to the "APP" nucleic acid or its complement under low stringency conditions,

(v) "APP-C99" (SEQ ID No: 3) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "APP-C99" encoded by a nucleic acid that hybridizes to the "APP-C99" nucleic acid or its complement under low stringency conditions,

(vi) "calsyntenin 1 " (SEQ ID No: 9) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "calsyntenin 1 "

encoded by a nucleic acid that hybridizes to the "calsyntenin 1" nucleic acid or its complement under low stringency conditions,

(vii) "IL13RA2" (SEQ ID No: 41) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "IL13RA2" encoded by a nucleic acid that hybridizes to the "IL13RA2" nucleic acid or its complement under low stringency conditions,

(viii) "ITM2C" (SEQ ID No: 17) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "ITM2C" encoded by a nucleic acid that hybridizes to the "ITM2C" nucleic acid or its complement under low stringency conditions,

(ix) "Neurotrypsin" (SEQ ID No: 24) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Neurotrypsin" encoded by a nucleic acid that hybridizes to the "Neurotrypsin" nucleic acid or its complement under low stringency conditions,

(x) "Paladin" (SEQ ID No: 85) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Paladin" encoded by a nucleic acid that hybridizes to the "Paladin" nucleic acid or its complement under low stringency conditions,

(xi) "Reelin" (SEQ ID No: 342) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "Reelin" encoded by a nucleic acid that hybridizes to the "Reelin" nucleic acid or its complement under low stringency conditions,

(xii) "RetSDR2" (SEQ ID No: 27) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "RetSDR2" encoded by a nucleic acid that hybridizes to the "RetSDR2" nucleic acid or its complement under low stringency conditions,

(xiii) "SORL1" (SEQ ID No: 30) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "SORL1" encoded by a nucleic acid that hybridizes to the "SORL1" nucleic acid or its complement under low stringency conditions,

(xiv) "TJP4" (SEQ ID No: 377) or a functionally active derivative thereof, or a functionally active fragment thereof, or a homolog thereof, or a variant of "TJP4" encoded by a nucleic acid that hybridizes to the "TJP4" nucleic acid or its complement under low stringency conditions, as a target for an active agent of a pharmaceutical, preferably a

drug target in the treatment or prevention of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease.

## **5. PROTOCOLS:**

The TAP-technology, which is more fully described in EP 1 105 508 B1 and in Rigaut, et al., 1999, Nature Biotechnol. 17:1030-1032 respectively was used and further adapted as described below for protein purification. Proteins were identified using mass spectrometry as described further below.

### **5.1 Construction of TAP-tagged bait**

The cDNAs encoding the complete ORF were obtained by RT-PCR. Total RNA was prepared from appropriate cell lines using the RNeasy Mini Kit (Qiagen). Both cDNA synthesis and PCR were performed with the SUPERSCRIPT One-Step RT-PCR for Long templates Kit (Life Technologies) using gene-specific primers. After 35-40 cycles of amplification PCR-products with the expected size were gel-purified with the MinElute PCR Purification Kit (Qiagen) and, if necessary, used for further amplification. Low-abundant RNAs were amplified by nested PCR before gel-purification. Restriction sites for NotI were attached to PCR primers to allow subcloning of amplified cDNAs into the retroviral vectors pIE94-N/C-TAP thereby generating N- or C-terminal fusions with the TAP-tag (Rigaut et al., 1999, Nature Biotechnol. 17:1030-1032).

The entry points (

BACE1, BACE2, APP, APP-C99, APP-C59, Psen-1, Psen-2, Nicastin, Aph-1a, Pen-2, CtnnB1, X11-beta, Fe65, Fe65L2, DAB1, JIP1, TIP60, GSK3a, Tau, FKRP, PTK7) were tagged at the N- and/or C-terminal end.

Clones were analyzed by restriction digest, DNA sequencing and by in vitro translation using the TNT T7 Quick Coupled Transcription/Translation System (Promega inc.). The presence of the proteins was proven by Western blotting using the protein A part of the TAP-tag for detection. Briefly, separation of proteins by standard SDS-PAGE was followed by semi-dry transfer onto a nitrocellulose membrane (PROTRAN, Schleicher&Schuell) using the MultiphorII blotting apparatus from Pharmacia Biotech.

The transfer buffer consisted of 48 mM Tris, 39 mM glycine, 10% methanol and 0,0375% sodium dodecylsulfate. After blocking in phosphate-buffered saline (PBS) supplemented with 10% dry milk powder and 0,1% Tween 20 transferred proteins were probed with the Peroxidase-Anti-Peroxidase Soluble Complex (Sigma) diluted in blocking solution. After intensive washing immunoreactive proteins were visualized by enhanced chemiluminescence (ECL; Amersham Pharmacia Biotech).

## 5.2 Preparation of Virus and infection

As a vector, a MoMLV-based recombinant virus was used.

The preparation has been carried out as follows:

### 5.2.1 Preparation of Virus

293 gp cells were grown to 100% confluency. They were split 1:5 on poly-L-Lysine plates (1:5 diluted poly-L-Lysine [0.01% stock solution, Sigma P-4832] in PBS, left on plates for at least 10 min.). On Day 2, 63 microgram of retroviral Vector DNA together with 13 microgram of DNA of plasmid encoding an appropriate envelope protein were transfected into 293 gp cells (Somia, et al., 1999, Proc. Natl. Acad. Sci. USA 96:12667-12672; Somia, et al. 2000, J. Virol. 74:4420-4424). On Day 3, the medium was replaced with 15 ml DMEM + 10% FBS per 15-cm dish. On Day 4, the medium containing viruses (supernatant) was harvested (at 24 h following medium change after transfection). When a second collection was planned, DMEM 10 % FBS was added to the plates and the plates were incubated for another 24 h. All collections were done as follows: The supernatant was filtered through 0.45 micrometer filter (Corning GmbH, cellulose acetate, 431155). The filter was placed into konical polyallomer centrifuge tubes (Beckman, 358126) that are placed in buckets of a SW 28 rotor (Beckman). The filtered supernatant was ultracentrifuged at 19400 rpm in the SW 28 rotor, for 2 hours at 21 degree Celsius. The supernatant was discarded. The pellet containing viruses was resuspended in a small volume (for example 300 microliter) of Hank's Balanced Salt Solution [Gibco BRL, 14025-092], by pipetting up and down 100-times, using an aerosol-safe tip. The viruses were used for transfection as described below.

### **5.2.2 Infection**

Cells that were infected were plated one day before into one well of a 6-well plate. 4 hours before infection, the old medium on the cells was replaced with fresh medium. Only a minimal volume was added, so that the cells are completely covered (e.g. 700 microliter). During infection, the cells were actively dividing.

A description of the cells and their growth conditions is given in 5.2.3

To the concentrated virus, polybrene (Hexadimethrine Bromide; Sigma, H 9268) was added to achieve a final concentration of 8 microgram/ml (this is equivalent to 2.4 microliter of the 1 milligram/ml polybrene stock per 300 microliter of concentrated retrovirus). The virus was incubated in polybrene at room temperature for 1 hour. For infection, the virus/polybrene mixture was added to the cells and incubated at 37 degree Celsius at the appropriate CO<sub>2</sub> concentration for several hours (e.g. over-day or overnight). Following infection, the medium on the infected cells was replaced with fresh medium. The cells were passaged as usual after they became confluent. The cells contain the retrovirus integrated into their chromosomes and stably express the gene of interest.

### **5.2.3 Cell lines**

The following cell lines were used:

For expression, SKN-BE2 cells were used. SKN-BE2 cells (American Type Culture Collection-No. CRL-2271) were grown in 95% OptiMEM + 5% iron-supplemented calf serum.

LAN-cells (human neuroblastoma cells) were grown in 90% RPMI 1640 + 10% FBS

The expression pattern of the TAP-tagged proteins was checked by immunoblot-analysis as described in 5.3.3 and/or by immunofluorescence as described in 5.3.1 or 5.3.2.

### **5.3 Checking of expression pattern of TAP-tagged proteins**

The expression pattern of the TAP-tagged protein was checked by immunoblot analysis and/or by immunofluorescence. Immunofluorescence analysis was either carried out according to section 5.3.1 or to section 5.3.2 depending on the type of the TAP-tagged protein. Immunoblot analysis was carried out according to section 5.3.3.

#### **5.3.1 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for plasma membrane and ER bound proteins**

Cells were grown in FCS media on polylysine coated 8 well chamber slides to 50% confluency. Then fixation of the cells was performed in 4% ParaFormAldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4). The cells were incubated for 30 minutes at room temperature in 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Blocking was performed with 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at room temperature. Incubation of the primary antibodies was performed in the blocking solution overnight at +4°C. The proper dilution of the antibodies was determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin for 2x 20 minutes at room temperature. Incubation of the secondary antibodies is performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes). Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin was used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were then washed again 2x 20 minutes at room temperature in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories)..

#### **5.3.2 Protocol for the indirect Immunofluorescence staining of fixed mammalian cells for non-plasma membrane bound proteins:**

Cells were grown in FCS media on Polylysine coated 8 well chamber slides to 50% confluence. Fixation of the cells was performed in 4% ParaFormAldehyde diluted in Phosphate Buffer Saline (PBS) solution (0.14M Phosphate, 0.1M NaCl pH 7.4) for 30 minutes at Room Temperature (RT), 300 microliters per well. Quenching was performed in 0.1M Glycine in PBS for 2x 20 minutes at room temperature. Permeabilization of cells was done with 0.5% Triton X-100 in PBS for 10 minutes at room temperature. Blocking was then done in 1% Bovine Serum Albumin (BSA) in 0.3% Saponin + PBS for at least 1 hour at RT (Blocking solution). Incubation of the primary antibodies was performed in the blocking solution, overnight at +4°C. The proper dilution of the antibodies has to be determined in a case to case basis. Cells were washed in PBS containing 0.3% Saponin, for 2x 20 minutes at RT. Incubation of the secondary antibodies was performed in the blocking solution. Alexa 594 coupled goat anti-rabbit is diluted 1:1000 (Molecular Probes), Alexa 488 coupled goat anti-mouse is diluted 1:1000 (Molecular Probes). DAPI was used to label DNA. If Phalloidin is used to label F-actin, the drug is diluted 1:500 and incubated with the secondary antibodies. Cells were washed 2x 20 minutes at RT in PBS. The excess of buffer was removed and cells were mounted in a media containing an anti-bleaching agent (Vectashield, Vector Laboratories).

### 5.3.3 Immunoblot analysis

To analyze expression levels of TAP-tagged proteins, a cell pellet (from a 6-well dish) was lysed in 60  $\mu$ l DNase I buffer (5% Glycerol, 100 mM NaCl, 0.8 % NP-40 (IGEPAL), 5 mM magnesium sulfate, 100  $\mu$ g/ml DNase I (Roche Diagnostics), 50 mM Tris, pH 7.5, protease inhibitor cocktail) for 15 min on ice. Each sample was split into two aliquots. The first half was centrifuged at 13,000 rpm for 5 min. to yield the NP-40-extractable material in the supernatant; the second half (total material) was carefully triturated. 50  $\mu$ g each of the NP-40-extractable material and the total material are mixed with DTT-containing sample buffer for 30 min at 50°C on a shaker and separated by SDS polyacrylamide gel electrophoresis on a precast 4-12% Bis-Tris gel (Invitrogen). Proteins were then transferred to nitrocellulose using a semi-dry procedure with a discontinuous buffer system. Briefly, gel and nitrocellulose membrane were stacked between filter papers soaked in either anode buffer (three layers buffer A1 (0.3 M Tris-HCl) and three

layers buffer A2 (0.03 M Tris-HCl)) or cathode buffer (three layers of 0.03 M Tris-HCl, pH 9.4, 0.1 % SDS, 40 mM  $\epsilon$ -aminocapronic acid). Electrotransfer of two gels at once was performed at 600 mA for 25 min. Transferred proteins were visualized with Ponceau S solution for one min to control transfer efficiency and then destained in water. The membrane was blocked in 5% non-fat milk powder in TBST (TBS containing 0.05% Tween-20) for 30 min at room temperature. It was subsequently incubated with HRP-coupled PAP antibody (1:5000 diluted in 5% milk/TBST) for 1 h at room temperature, washed three times for 10 min in TBST. The blot membrane was finally soaked in chemiluminescent substrate (ECL, Roche Diagnostics) for 2 min. and either exposed to X-ray film or analyzed on an imaging station.

#### 5.4 Purification of protein complexes

Protein complex purification was adapted to the sub-cellular localization of the TAP-tagged protein and was performed as described below.

##### 5.4.1 Lysate preparation for cytoplasmic proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scrapper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of CZ lysis buffer (50 mM Tris-Cl, pH 7.4; 5 % Glycerol; 0,2 % IGEPAL; 1.5 mM MgCl<sub>2</sub>; 100 mM NaCl; 25 mM NaF; 1 mM Na<sub>3</sub>VO<sub>4</sub>; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was incubated for 30 min on ice and spun for 10 min at 20,000g. The supernatant was subjected to an additional ultracentrifugation step for 1 h at 100,000g. The supernatant was recovered and rapidly frozen in liquid nitrogen or immediately processed further.

##### 5.4.2 Lysate preparation for membrane proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scrapper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Membrane-Lysis buffer (50 mM Tris, pH 7.4; 7.5 % Glycerol; 1 mM EDTA; 150 mM NaCl; 25 mM NaF; 1 mM Na<sub>3</sub>VO<sub>4</sub>; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 750g, the supernatant was recovered and subjected to an ultracentrifugation step for 1 h at 100,000g. The membrane pellet was resuspended in 7.5 ml of Membrane-Lysis buffer containing 0.8% n-Dodecyl-β-D-maltoside and incubated for 1 h at 4°C with constant agitation. The sample was subjected to another ultracentrifugation step for 1h at 100,000g and the solubilized material was quickly frozen in liquid nitrogen or immediately processed further.

#### 5.4.3 Lysate preparation for nuclear proteins

About  $1 \times 10^9$  adherent cells (average) were harvested with a cell scrapper and washed 3 times in ice-cold PBS (3 min, 550g). Collected cells were frozen in liquid nitrogen or immediately processed further. For cell lysis, the cell pellet was resuspended in 10 ml of Hypotonic-Lysis buffer (10 mM Tris, pH 7.4; 1.5 mM MgCl<sub>2</sub>; 10 mM KCl; 25 mM NaF; 1 mM Na<sub>3</sub>VO<sub>4</sub>; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and homogenized by 10 strokes of a tight-fitted pestle in a dounce homogenizer. The lysate was spun for 10 min at 2,000g and the resulting supernatant (S1) saved on ice. The nuclear pellet (P1) was resuspended in 5 ml Nuclear-Lysis buffer (50 mM Tris, pH 7.4; 1.5 mM MgCl<sub>2</sub>; 20 % Glycerol; 420 mM NaCl; 25 mM NaF; 1 mM Na<sub>3</sub>VO<sub>4</sub>; 1 mM DTT; containing 1 tablet of EDTA-free Protease inhibitor cocktail (Complete™, Roche) per 25 ml of buffer) and incubated for 30 min on ice. The sample was combined with S1, further diluted with 7 ml of Dilution buffer (110 mM Tris, pH 7.4; 0.7 % NP40; 1.5 mM MgCl<sub>2</sub>; 25 mM NaF; 1 mM Na<sub>3</sub>VO<sub>4</sub>; 1 mM DTT), incubated on ice for 10 min and centrifuged at 100,000g for 1h. The final supernatant (S2) was frozen quickly in liquid nitrogen.

#### 5.4.4 Tandem Affinity Purification

The frozen lysate was quickly thawed in a 37°C water bath, and spun for 20 min at 100,000g. The supernatant was recovered and incubated with 0.2 ml of settled rabbit IgG-Agarose beads (Sigma) for 2 h with constant agitation at 4°C. Immobilized protein complexes were washed with 10 ml of CZ lysis buffer (containing 1 Complete™ tablet (Roche) per 50 ml of buffer) and further washed with 5 ml of TEV cleavage buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 0.5 mM EDTA; 1 mM DTT). Protein-complexes were eluted by incubation with 5 µl of TEV protease (GibcoBRL, Cat.No. 10127-017) for 1 h at 16°C in 150 µl TEV cleavage buffer. The eluate was recovered and combined with 0.2 ml settled Calmodulin affinity beads (Stratagene) in 0.2 ml CBP binding buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 2mM MgAc; 2mM Imidazole; 1mM DTT; 4 mM CaCl<sub>2</sub>) followed by 1 h incubation at 4°C with constant agitation. Immobilized protein complexes were washed with 10 ml of CBP wash buffer (10 mM Tris, pH 7.4; 100 mM NaCl; 0.1 % IGEPAL; 1mM MgAc; 1mM Imidazole; 1mM DTT; 2 mM CaCl<sub>2</sub>) and eluted by addition of 600 µl CBP elution buffer (10 mM Tris, pH 8.0; 5 mM EGTA) for 5 min at 37°C. The eluate was recovered in a siliconized tube and lyophilized. The remaining Calmodulin resin was boiled for 5 min in 50 µl 4x Laemmli sample buffer. The sample buffer was isolated, combined with the lyophilised fraction and loaded on a NuPAGE gradient gel (Invitrogen, 4-12%, 1.5 mm, 10 well).

#### 5.4.5 Isolation of the Sambiasin complex of the invention from mouse tissue

Two mouse forebrains (0.6314 g total wet weight) were lysed in 14 mls of 50 mM HEPES pH 7.4; 150 mM NaCl; 1 mM EDTA; 0.5 mM Sodium Vanadate; 10% Glycerol; 1% n-Dodecyl-β-D-maltoside containing standard proteinase inhibitors. The tissue was homogenised in a Warring blender for 30 seconds on ice. Homogenates were incubated on ice for 1 hour and then centrifuged at 13,000 g for 30 min at 4°C. The resulting pellet was stored at -80°C while the supernatant was centrifuged at 50,000 g for 30 min at 4°C and the resulting pellet was also stored at -80°C. 6.5 ml of the supernatant from this second centrifugation step was taken and combined with 25 µl of anti presenilin-1 antisera (MAB5232, Chemicon). The antibody/lysate mixture was incubated for 1 hour at 4°C with end-over end mixing. Pre-washed protein G sepharose was added and the

mixture was incubated overnight at 4°C with end-over mixing. The protein G was recovered by centrifugation at 200 g for 5 min at 4°C. The protein G beads were then washed 5 times in 1ml lysis buffer (containing 0.1% n-Dodecyl-β-D-maltoside rather than 1%). 100 µl of NuPAGE sample buffer (Invitrogen) was added and the sample incubated at 37°C for 10 min. Samples were separated on 4-12 % NuPAGE bis/tris gels (Invitrogen, 1.5 mm, 10 well). Proteins were visualized by staining with colloidal coomassie (Sigma) and then analysed by LC/MSMS.

### 5.5 Protein identification by mass spectrometry

#### 5.5.1 Protein digestion prior to mass spectrometric analysis

Gel-separated proteins were reduced, alkylated and digested in gel essentially following the procedure described by Shevchenko et al., 1996, Anal. Chem. 68:850-858. Briefly, gel-separated proteins were excised from the gel using a clean scalpel, reduced using 10 mM DTT (in 5mM ammonium bicarbonate, 54°C, 45 min) and subsequently alkylated with 55 mM iodoacetamid (in 5 mM ammonium bicarbonate) at room temperature in the dark (30 min). Reduced and alkylated proteins were digested in gel with porcine trypsin (Promega) at a protease concentration of 12.5 ng/µl in 5mM ammonium bicarbonate. Digestion was allowed to proceed for 4 hours at 37°C and the reaction was subsequently stopped using 5 µl 5% formic acid.

#### 5.5.2 Sample preparation prior to analysis by mass spectrometry

Gel plugs were extracted twice with 20 µl 1% TFA and pooled with acidified digest supernatants. Samples were dried in a vacuum centrifuge and resuspended in 13 µl 1% TFA.

#### 5.5.3 Mass spectrometric data acquisition

Peptide samples were injected into a nano LC system (CapLC, Waters or Ultimate, Dionex) which was directly coupled either to a quadrupole TOF (QTOF2, QTOF Ultima, QTOF Micro, Micromass or QSTAR Pulsar, Sciex) or ion trap (LCQ Deca XP) mass spectrometer. Peptides were separated on the LC system using a gradient of aqueous and organic solvents (see below). Solvent A was 5% acetonitrile in 0.5% formic acid and solvent B was 70% acetonitrile in 0.5% formic acid.

Time (min)	% solvent A	% solvent B
0	95	5
5.33	92	8
35	50	50
36	20	80
40	20	80
41	95	5
50	95	5

Peptides eluting off the LC system were partially sequenced within the mass spectrometer.

#### 5.5.4 Protein identification

The peptide mass and fragmentation data generated in the LC-MS/MS experiments were used to query fasta formatted protein and nucleotide sequence databases maintained and updated regularly at the NCBI (for the NCBInr, dbEST and the human and mouse genomes) and European Bioinformatics Institute (EBI, for the human, mouse, *D. melanogaster* and *C. elegans* proteome databases). Proteins were identified by correlating the measured peptide mass and fragmentation data with the same data computed from the entries in the database using the software tool Mascot (Matrix Science; Perkins et al., 1999, Electrophoresis 20:3551-3567). Search criteria varied depending on which mass spectrometer was used for the analysis.

TABLE 1

## COMPONENTS OF COMPLEXES

Name of complex	Entry Point	All Interactors of the complex	known interactors of the complex	Novel interactors of the complex
aph-1a-complex	aph-1a	APP APP-C99 JUP Nicastrin Psen1 ACAT1 BRI calsyntenin 1 CGI-13 CPD DLK1 DSCD75 Endo180 FACL3 FLJ10579 ITM2C ITPR1 KIAA0062 Zn transp KIAA0363 KIAA1949 KiDins220 MDR1 Neurotrypsin PLD3 PP2Cg RetSDR2 SARM SFXN1 SORL1 SPC18 SPC22 SPC25 SPTLC2 stearoyl-CoA desaturase TMP21 VLCAD YME1L1	APP	
APP-complex	APP	APP-C99 Fe65	APP-C99 Fe65	

		Fe65L1		Fe65L1
		BRI		BRI
		IL13RA2		IL13RA2
		ITM2C		ITM2C
		LAPTM4B		LAPTM4B
		S100alpha		S100alpha
		S100beta		S100beta
APP-C59-complex	APP-C59	Fe65	Fe65	Fe65L1
		Fe65L1		COPS3
		COPS3		Cullin-3
		Cullin-3		nardilysin
		nardilysin		S100alpha
		S100alpha		S100beta
		S100beta		visinin-like 1
APP-C99-complex	APP-C99	APP	APP	
		Fe65		Fe65
		Fe65L1		Fe65L1
		BRI		BRI
		Caldesmon		Caldesmon
		calsyntenin 1		calsyntenin 1
		CNIP		CNIP
		CPD		CPD
		DLK1		DLK1
		GPR49		GPR49
		IL13RA2		IL13RA2
		ITM2C		ITM2C
		KIAA1949		KIAA1949
		LAPTM4B		LAPTM4B
		Nap1-like		Nap1-like
		S100alpha		S100alpha
		S100beta		S100beta
		visinin-like 1		visinin-like 1
BACE1-complex	BACE1	APP	APP	
		Nicastrin		Nicastrin
		ACAT1		ACAT1
		APLP2		APLP2
		BRI		BRI
		calsyntenin 1		calsyntenin 1
		CELSR2		CELSR2
		CGI-13		CGI-13
		DLK1		DLK1
		DSCD75		DSCD75
		FADS2		FADS2
		GPR49		GPR49
		ITM2C		ITM2C
		KiDins220		KiDins220

		LAPTM4B		LAPTM4B
		Neurotrypsin		Neurotrypsin
		NogoA		NogoA
		OS-9		OS-9
		PDGFRB		PDGFRB
		PTK7		PTK7
		RetSDR2		RetSDR2
		S100alpha		S100alpha
		SORL1		SORL1
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		TMP21		
		UGCGL1		
BACE2- complex	BACE2	Nicastrin	Nicastrin	APLP2
		APLP2		BRI
		BRI		calsyntenin 1
		calsyntenin 1		CGI-13
		CGI-13		DLK1
		DLK1		DSCD75
		DSCD75		IL13RA2
		IL13RA2		ITM2C
		ITM2C		ODZ3
		ODZ3		PLD3
		PLD3		stearoyl-CoA desaturase
		stearoyl-CoA desaturase		TMP21
		TMP21		
BRI-complex	BRI	APP	APP	
		APP-C99		APP-C99
		CPD		CPD
		ITM2C		ITM2C
CtnnB1- complex	CtnnB1	Psen1	Psen1	
		APC		APC
		CtnnA1		CtnnA1
		CtnnA2		CtnnA2
		CtnnD1		CtnnD1
		JUP		JUP
		NCadh		NCadh
		TCF-4		TCF-4
		ArmVCF		ArmVCF
DAB1- complex	DAB1	APLP1	APLP1	
		APP		APP
		APP-C99		APP-C99
		DAB2IP		DAB2IP
		PP2a PR55a		PP2a PR55a
		CK1 delta		CK1 delta

		CRK		CRK
		FYN		FYN
		HSP105		HSP105
		PP2a cat beta		PP2a cat beta
		PP2a PR65		PP2a PR65
		S100alpha		S100alpha
		S100beta		S100beta
Fe65-complex	Fe65	TIP60	TIP60	
		APLP1		APLP1
		APLP2		APLP2
		APP		APP
		APP-C99		APP-C99
		Paladin		Paladin
		S100alpha		S100alpha
		S100beta		S100beta
		SAP62		SAP62
		visinin-like 1		visinin-like 1
Fe65L2-complex	Fe65L2	APLP2	APLP2	
		APP		APP
		APP-C99		APP-C99
		COPS1		COPS1
		COPS2		COPS2
		COPS3		COPS3
		COPS3		COPS3
		COPS4		COPS4
		COPS5		COPS5
		COPS6		COPS6
		COPS7b		COPS7b
		COPS8		COPS8
		Cullin-3		Cullin-3
		Nedd8		Nedd8
		Paladin		Paladin
		RBX1		RBX1
		RHOBTB1		RHOBTB1
		RHOBTB2		RHOBTB2
		S100alpha		S100alpha
		S100beta		S100beta
		TNRC15		TNRC15
		visinin-like 1		visinin-like 1
FKRP-complex	FKRP	CLGN	CLGN	
		DSCD75		DSCD75
		EXTL2		EXTL2
		ITM2C		ITM2C
		ITPR1		ITPR1
		KIAA0062 Zn transp		KIAA0062 Zn transp
		KiDins220		KiDins220

		Neurotrypsin	Neurotrypsin
		PP2Cg	PP2Cg
		SORL1	SORL1
		TLOC1	TLOC1
		UGCGL1	UGCGL1
		Wolframin	Wolframin
GSK3a-complex	GSK3a	Axin	Axin
		FRAT1	FRAT1
		FRAT2	FRAT2
		rAxin1	rAxin1
		AKAP11	AKAP11
		C14orf129 (DUF727)	C14orf129 (DUF727)
		calcineurin A alpha	calcineurin A alpha
		calcineurin A beta	calcineurin A beta
		cdc37	cdc37
		DSCR1	DSCR1
		Nap1-like	Nap1-like
		PKA cat alpha	PKA cat alpha
		PKA cat beta	PKA cat beta
		PKA reg I alpha	PKA reg I alpha
		PP2a B56 gamma	PP2a B56 gamma
		PP2a cat beta	PP2a cat beta
		PP2a PR65	PP2a PR65
		TcD37/prune	TcD37/prune
JIP1-complex	JIP1	KLC1	KLC1
		nKHC2	nKHC2
		uKHC	uKHC
Nicastrin-complex	Nicastrin	Nicastrin	Nicastrin
		Psen1	Psen1
		aph-1a	aph-1a
		APP	APP
		CtnnA1	CtnnA1
		CtnnA2	CtnnA2
		CtnnB1	CtnnB1
		CtnnD1	CtnnD1
		JUP	JUP
		NCadh	NCadh
		ACAT1	ACAT1
		CGI-13	CGI-13
		CK2B	CK2B
		CLGN	CLGN
		ECSIT	ECSIT
		FACL3	FACL3
		FADS2	FADS2
		FLJ20481	FLJ20481
		ITM2C	ITM2C

		ITPR1		ITPR1
		KIAA0363		KIAA0363
		MDR1		MDR1
		Neurotrypsin		Neurotrypsin
		PTP LOC114971		PTP LOC114971
		RetSDR2		RetSDR2
		SFXN1		SFXN1
		SPC18		SPC18
		SPC22		SPC22
		SPC25		SPC25
		SPTLC2		SPTLC2
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		STT3		STT3
		TMP21		TMP21
		UGCGL1		UGCGL1
		visinin-like 1		visinin-like 1
		Wolframin		Wolframin
		YME1L1		YME1L1
pen-2-complex	pen-2	CtnnD1	CtnnD1	
		Nicastrin		Nicastrin
		Psen1		Psen1
		ACAT1		ACAT1
		CaMKIIa		CaMKIIa
		copine III		copine III
		FKRP		FKRP
		FLJ10579		FLJ10579
		FLJ20481		FLJ20481
		KIAA1102		KIAA1102
		KIAA1949		KIAA1949
		MDR1		MDR1
		Neurotrypsin		Neurotrypsin
		S100alpha		S100alpha
		SFXN1		SFXN1
		SPC22		SPC22
		SPC25		SPC25
		STT3		STT3
		TMP21		TMP21
		Wolframin		Wolframin
Psen1-complex	Psen1	Psen1	Psen1	
		aph-1a		aph-1a
		CtnnA1		CtnnA1
		CtnnA2		CtnnA2
		CtnnB1		CtnnB1
		CtnnD1		CtnnD1
		JUP		JUP
		NCadh		NCadh
		Nicastrin		Nicastrin

		pen-2		pen-2
		CaMKIIa		CaMKIIa
		DSCD75		DSCD75
		ECSIT		ECSIT
		FKRP		FKRP
		FLJ10579		FLJ10579
		FLJ20481		FLJ20481
		KIAA0090		KIAA0090
		MDR1		MDR1
		SARM		SARM
		SFXN1		SFXN1
		SORT1		SORT1
		SPC25		SPC25
		STT3		STT3
		TMP21		TMP21
		VLCAD		VLCAD
		YME1L1		YME1L1,
Psen2-complex	Psen2	aph-1a	aph-1a	
		Nicastrin		Nicastrin
		Nicastrin		Nicastrin
		CGI-13		CGI-13
		DSCD75		DSCD75
		ECSIT		ECSIT
		FACL3		FACL3
		FADS2		FADS2
		FLJ10579		FLJ10579
		FLJ20481		FLJ20481
		ITPR1		ITPR1
		KIAA0090		KIAA0090
		MDR1		MDR1
		NicAChRa3		NicAChRa3
		PLD3		PLD3
		SFXN1		SFXN1
		SLC4A2		SLC4A2
		SORT1		SORT1
		SPC18		SPC18
		SPC22		SPC22
		SPC25		SPC25
		SPTLC2		SPTLC2
		stearoyl-CoA desaturase		stearoyl-CoA desaturase
		STT3		STT3
		TMP21		TMP21
		VLCAD		VLCAD
		Wolframin		Wolframin
		YME1L1		YME1L1
PTK7-complex	PTK7	APP	APP	
		BRI		BRI

		CELSR2		CELSR2
		DLK1		DLK1
		FADS2		FADS2
		HIFPH3/EGLN3		HIFPH3/EGLN3
		ITM2C		ITM2C
		Nap1-like		Nap1-like
		Reelin		Reelin
SPPL3-complex	SPPL3	APP-C99	APP-C99	
		APP		APP
		ECSIT		ECSIT
		Nap1-like		Nap1-like
		NicAChRa3		NicAChRa3
tau-complex	tau	14-3-3 zeta	14-3-3 zeta	
		PP2a PR55a		PP2a PR55a
		HSP105		HSP105
		PP2a cat beta		PP2a cat beta
		PP2a PR65		PP2a PR65
TIP60-complex	TIP60	BAF53	BAF53	
		Fe65		Fe65
		Fe65L1		Fe65L1
		TRRAP		TRRAP
		DLK1		DLK1
		DMAP1		DMAP1
		EP400		EP400
		TCFL1/YL1		TCFL1/YL1
X11beta-complex	X11beta	APLP1	APLP1	
		APLP2		APLP2
		APP		APP
		APP-C99		APP-C99
		calsyntenin 1		calsyntenin 1
		IL13RA2		IL13RA2
		ITM2C		ITM2C
		Neurotrypsin		Neurotrypsin
		Paladin		Paladin
		Reelin		Reelin
		RetSDR2		RetSDR2
		SORL1		SORL1
		TJP4		TJP4

TABLE 2

## INDIVIDUAL PROTEINS OF THE COMPLEXES

Protein name	SEQ ID	IPI number	Molecular weight
aph-1a	1	IPI00059964.1	28996
APP	2	IPI00006608.1	86943
APP-C99	3		11278
JUP	4	IPI00028128.1	81498
Nicastrin	5	IPI00021983.1	78411
Psen1	6	IPI00028077.1	52668
ACAT1	7	IPI00019898.3	64833
BRI	8	IPI00031821.1	30338
calsyntenin 1	9	IPI00218869.1	108670
CGI-13	10	IPI00008847.1	52917
CPD	11	IPI00027078.2	152915
DLK1	12	IPI00218210.1	32910
DSCD75	13	IPI00010292.1	23865
Endo180	14	IPI00005707.3	166655
FACL3	15	IPI00031397.1	80346
FLJ10579	16	IPI00018730.1	52118
ITM2C	17	IPI00016014.1	30224
ITPR1	18	IPI00216955.1	314758
KIAA0062 Zn transp	19	IPI00014236.2	62461
KIAA0363	20	IPI00004538.1	156999
KIAA1949	21	IPI00152853.1	73064
KiDins220	22	IPI00033429.1	197211
MDR1	23	IPI00027481.1	141463
Neurotrypsin	24	IPI00011063.2	97067
PLD3	25	IPI00163951.2	49573
PP2Cg	26	IPI00006167.1	59272
RetSDR2	27	IPI00008260.1	32964
SARM	28	IPI00007919.1	75337
SFXN1	29	IPI00009368.2	35619

SORL1	30	IPI00022608.1	248441
SPC18	31	IPI00104128.1	20625
SPC22	32	IPI00030262.2	20253
SPC25	33	IPI00220125.1	25692
SPTLC2	34	IPI0005751.1	62924
stearoyl-CoA desaturase	35	IPI00013007.2	41523
TMP21	36	IPI00028055.1	24976
VLCAD	37	IPI00163655.1	68788
YME1L1	38	IPI00099529.1	79832
Fe65	39	IPI00154492.2	77858
Fe65L1	40	IPI00023841.1	81080
IL13RA2	41	IPI00032199.1	44176
LAPTM4B	42	IPI00020093.1	31735
S100alpha	43	IPI00220412.1	10546
S100beta	44	IPI00220413.1	10713
APP-C59	45		6835
COPS3	46	IPI00025721.1	47873
Cullin-3	47	IPI00014312.1	88930
nardilysin	48	IPI00014521.1	130945
visinin-like 1	49	IPI00216313.1	22142
Caldesmon	50	IPI00221137.1	61213
CNIP	51	IPI00010625.1	59797
GPR49	52	IPI00021131.1	99998
Nap1-like	53	IPI00155244.1	44159
BACE1	54	IPI00216211.1	48212
APLP2	55	IPI00031030.1	86956
CELSR2	56	IPI00015346.1	317453
FADS2	57	IPI00183786.1	52259
NogoA	58	IPI00219209.1	106360
OS-9	59	IPI00218476.1	76295
PDGFRB	60	IPI00015902.2	124093
PTK7	61	IPI00219694.1	118392

UGCGL1	62	IPI00024466.1	177190
BACE2	63	IPI00001954.1	56180
ODZ3	64	IPI00165064.1	49073
CtnnB1	65	IPI00017292.1	
APC	66	IPI00215877.1	300455
CtnnA1	67	IPI00215948.1	102776
CtnnA2	68	IPI00030907.1	105282
CtnnD1	69	IPI00182469.2	107349
NCadh	70	IPI00015717.1	99851
TCF-4	71	IPI00164708.2	67919
ArmVCF	72	IPI00010490.1	104642
DAB1	73	IPI00123898.1	63578
APLP1	74	IPI00020012.2	72176
DAB2IP	75	IPI00045600.1	117651
PP2a PR55a	76	IPI00220836.2	52004
CK1 delta	77	IPI00011102.2	47330
CRK	78	IPI00004838.1	33872
FYN	79	IPI00031350.1	63754
HSP105	80	IPI00022080.1	96865
PP2a cat beta	81	IPI00008380.1	96865
PP2a PR65	82	IPI00101135.1	65309
Fe65	83	IPI00010843.1	77244
TIP60	84	IPI00165536.1	77244
Paladin	85	IPI00011063.2	97067
SAP62	86	IPI00017341.2	49256
Fe65L2	87	IPI00218296.2	53501
COPS1	88	IPI00156282.1	56481
COPS2	89	IPI00018813.1	51597
COPS4	90	IPI00171844.1	46269
COPS5	91	IPI00009958.3	37452
COPS6	92	IPI00163230.3	36163
COPS7b	93	IPI00033154.1	30277
COPS8	94	IPI00009480.1	23226

Nedd8	95	IPI00020008.1	9072
RBX1	96	IPI00003386.1	12274
RHOBTB1	97	IPI00001317.1	79417
RHOBTB2	98	IPI00187107.1	85137
TNRC15	99	IPI00169434.1	153494
FKRP	100	IPI00013281.1	54568
CLGN	101	IPI00183309.1	73577
EXTL2	102	IPI00002732.1	37466
ITM2C	103	IPI00016014.1	37466
TLOC1	104	IPI00019004.1	45862
Wolframin	105	IPI00008711.1	177190
GSK3a	106	IPI00028568.1	
Axin	107	IPI00005188.2	95635.
FRAT1	108	IPI00023762.1	29062
FRAT2	109	IPI00075185.1	24051
rAxin1	110		92285
AKAP11	111	IPI00007411.1	210512
C14orf129 (DUF727)	112	IPI00009374.2	15648
calcineurin A alpha	113	IPI00220616.1	63068
calcineurin A beta	114	IPI00218862.1	58013
cdc37	115	IPI00013122.1	44468
DSCR1	116	IPI00215936.1	22767
PKA cat alpha	117	IPI00219591.1	40590
PKA cat beta	118	IPI00027283.1	40491
PKA reg I alpha	119	IPI00021831.1	42982
PP2a B56 gamma	120	IPI00185637.2	52625
TcD37/prune	121	IPI00166931.1	50200
JIP1	122	IPI00023133.1	77524
KLC1	123	IPI00020096.1	64786
nKHC2	124	IPI00028561.1	109495
uKHC	125	IPI00012837.1	109685
CtnnB1	126	IPI00017292.1	85497
CK2B	127	IPI00010865.1	24942

ECSIT	128	IPI00106506.1	49148
FLJ20481	129	IPI00016418.1	47655
PTP LOC114971	130	IPI00174190.1	22844
STT3	131	IPI00102885.1	80530
pen-2	132	IPI00020516.1	12029
CaMKIIa	133	IPI00098624.1	59022
copine III	134	IPI00024403.1	60131
KIAA1102	135	IPI00167860.1	123943
KIAA0090	136	IPI00167111.1	111759
SORT1	137	IPI00016022.1	92100
Psen2	138	IPI00028485.1	50140
NicAChRa3	139	IPI00007259.1	55637
SLC4A2	140	IPI00337431.3	137009
HIFPH3/EGLN3	141	IPI00004971.1	52259
Reelin	142	IPI00021018.1	388402
SPPL3	143	IPI00152440.1	42563
tau	144	IPI00025499.1	45850
14-3-3 zeta	145	IPI00021263.1	27745
BAF53	146	IPI00003627.1	47461
TRRAP	147	IPI00144399.1	434414
DMAP1	148	IPI00219919.1	53462
EP400	149	IPI00064931.1	340147
TCFL1/YL1	150	IPI00020434.1	40594
X11beta	151	IPI00017817.1	
TJP4	152	IPI00010544.2	60705

TABLE 3

## BIOCHEMICAL ACTIVITIES OF THE COMPLEXES

Name of complex	Biochemical Activity
BACE1-complex	Beta-secretase activity
BACE2-complex	Secretase activity
APP-complex	Signalling activity (regulator of transcription)
APP-C99-complex	Signalling activity (regulator of transcription)
APP-C59-complex	Signalling activity (regulator of transcription)
Psen-1-complex	Gamma-secretase activity
Psen-2-complex	Gamma-secretase activity
Nicastrin-complex	Gamma-secretase activity and assembly (trafficking)
Aph-1a-complex	Gamma-secretase activity and assembly (trafficking)
Pen-2-complex	Gamma-secretase activity and assembly (trafficking)
CtnnB1-complex	General: Beta-catenin signaling; here: complex regulating stability of beta-catenin
X11beta-complex	Regulator of APP processing and APP function
Fe65-complex	Regulator of APP processing and APP function
Fe65L2-complex	Regulator of APP turnover, processing and signaling
DAB1-complex	Regulator of APP processing and/or signaling; Upstream activator of tau phosphorylation
JIP1-complex	Regulator of APP trafficking and signaling
TIP60-complex	Regulator or transcription
GSK3a-complex	Regulation of APP processing
Tau-complex	Regulator of microtubules and vesicle transport along microtubules
FKRP-complex	Glycosyltransferase complex; role in maturation of the gamma-secretase complex
PTK7-complex	Role in neuronal signal transduction; involved in neural development and structural plasticity of the CNS; modulator of BACE function.

26. März 2004

SEQUENCES

SEQ ID No: 1

MGAAVFFGCTFVAFGPAFALFLITVAGDPLRVIIILVAGAFFWLVSLLASVVFILHVTD  
RSDARLQYGLLIFGAAVSVLLQEVRFAYYKLLKADEGLASLSLEDGRSPISIRQMAYVS  
GLSGIISGVFSVINILADALGPGVVGIGHGDSPYYFLTSAAFLTAIIILLHTFWGVVFFDACE  
RRRYWALGLVVGSHLLTSLNTPWEASLLPIYAVTVSMGLWAFITAGGSLRSIQRS  
LLCRRQEDSRVMVYSALRIPPED

SEQ ID No: 2

MLPGLALLLAATARALEVPTDGNAGLLAEPQIAMFCGRLNMHMNVQNGKWDSDP  
GTKTCIDTKEGILQYCQEVEPELQITNVVEANQPVTIQNWCKRGRKQCKTHPHFVIPYR  
CLVGEFVSDALLVPDKCKFLHQERMDVCETHLHWHTVAKETCSEKSTNLHDYGMLLPC  
GIDKFRGVEFVCCPLAEESDNVDSADAEEEDSDVWWGGADTDYADGSEDKVVEVAEE  
EEVAEVEEEEADDDEDGDEVEEEAEPYEEATERTTSIATTTTTTESVEEVREV  
CSEQAETGPCRAMISRWYFDVTEGKCAPFFYGGCGGNRNNFDTEEYCMAVCGSAMS  
QSLLKTTQEPLARDPVKLPTTAASTPDAVKYLETPGDENEHAHFQKAKERLEAKHRER  
MSQVMREWEEAERQAKNLPKADKKAVIQHFQEKEVESLEQEAANERQQLVETHMARVE  
AMLNDRRRLALENYITALQAVPPRPRHVFNMLKKYVRAEQKDRQHTLKHFHVRMVDP  
KKAAQIRSQVMTHLRVIYERMNQSLSLYNVPAVAEEIQDEVDELLQKEQNYSDDVLAN  
MISEPRISYGNALMPSLTETKTTVELLPVNGEFSLDDLQPWHSGADSVPANTENEVE  
PVDARPAADRGLTRPGSGLTNIKTEEISEVKMDAEFRHDSGYEVHHQKLVFFAEDVGS  
NKGAIIGLMVGGVIATVIVITVMLKKQYTSIHGVVEVDAAVTPEERHLSKMQQNGY  
ENPTYKFFEQMQN

SEQ ID No: 3

MDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVIATVIVITVMLKKQYTSI  
HHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No: 4

EVMNLMEQPIKVTIEWQQTYTYDSGIHSGANTCVPSVSSKGIMEEDEACGRQYTLKKTT  
TYTQGVPPSQGDLEYQMSTTARA KRVREAMCPGVSGEGQLALLATQVEGQATNLQRL  
AEPSQLLKS AIVHLINYQDDAELVTRALPELTKLND EDPVVVTKAAMIVNQLSKKEASR  
RALMGSPQLVAAVVRTMQNTSDLDTARCTTSILHNLSHREGLLAIFKSGGIPALVRMLS

SPVESVLFYAITTLHNILLYQEGAKMACAGRRAQKMPVPLNKNNPKFLAITTDCLQLLAY  
 GNQESKLILANGGPQALVQIMRNYSYEKLLWTSRVLKVLSCPSNKPAAIVEAGGMQA  
 LGKHLTSNSPRLVQNCLWTLRNLSDVATKQEGLESVLKILVNQLSVDDNVLTCACTGTL  
 SNLTCNNSKNKTIVTQNNSGVEALIHALRAGDKDDITEPAVCALRHLSRHPPEAEMAQN  
 SVRLNYGIPAIVKLLNQPNQWPLVKATIGLIRNLALCPANHAPLQEAAVIPRLVQLLVKAH  
 QDAQRHVAAGTQQPYTDGVRMEEIVEGCTGALHILARDPMNRMEIFRLNTIPLFVQLLY  
 SSVENIQRVAAGVLCELAQDKEAADADAEGASAPLMELLHSRNEGTATYAAAVLFRISE  
 DKNPDYRKRVSELNSLFKHDPAAWEAQSMIPINEPYGDDMDATYRPMYSSDVPLD  
 PLEMHMDMDGDYPIDTYSDGLRPPYPTADHMLA

SEQ ID No: 5

MATAGGGSGADPGSRGLLRLSFCVLLAGLCRGNSVERKIYIPLNKTAPCVRLLNATHQI  
 GCQSSISGDTGVIHVVEKEEDLQWVLTDPNPPYMVLLESKHFTRDLMEKLKGRTSRIA  
 GLAVSLTKPSPASGFSPSVQCPNDGFGVYSNSYGPEFAHCRCIQWNNSLGNGLAYERDFS  
 FPIFLLEDENETKVIKQCYQDHNLSQNGSAPTFPLCAMQLFSHMHAVISTATCMRRSSIQ  
 STFSINPEIVCDPLSDYNVWSMLKPINTTGTLPDDRVVVAATRLDSRSFFWNVAPGAE  
 SAVASFVTQLAAEALQKADVTTLPRNVMVFFQGETFDYIGSSRMVYDMEKGKFV  
 QLENVDSFVELGQVALRTSLELWMHTDPVSQKNESVRNQVEDLLATEKSGAGVPAV  
 LRRPNQSQPLPPSSLQRFLRARNISGVVLADHSGAFHNKYYQSIYDTAENINVSYPEWL  
 SPEEDLNFTVDTAKALADVATVLGRALYELAGGTNFSDTVQADPQTVTRLLYGFlikan  
 NSWFQSILRQDLRSYLGDPQLQHYIAVSSPTNTYVVQYALANLTGTVVNLREQCQDP  
 SKVPSENKDLYEYSWVQGPLHSNETDRLPPRCVRSTARLARALSPAELSQWSSTEYST  
 WTESRWKDIRARIFLIASKELELITLTVGFGILIFSLIVTYCINAKADVLFIAPREPGAVSY

SEQ ID No: 6

MTELPAPLSYFQNAQMSEDNHLSNTVRSQNDNRERQEHNDRRSLGHPEPLSNGRPQ  
 GNSRQVVEQDEEEDEELTLKYGAKHVIMLFVPVTLCKMVVVVATIKSVSFYTRKDQQLIYT  
 PFTEDTETVGQRALHSILNAAIMISVIVVMTILLVLYKYRCYKVIAHWLISSLLLFFF  
 YLGEVFKTYNVAVDYITVALLIWNFGVVGMSIHWKGPLRLQQAYLIMISALMALVFIKYL  
 EWTAWLILAVISVYDLVAVLCPKGPLRMLVETAQERNETLFPALIYSSTMVWLVNMAEG  
 DPEAQRRVSKNSKNAESTERESQDTVAENDDGGFSEWEAQRDSHLGPHRSTPES  
 RAAVQELSSILAGEDPEERGVKLGLGDFIFYSVLVGKASATASGDWNTTIACFVAILIGL  
 CLTLLLAIFKKALPALPISITFGLVFYFATDYLVQPFMDQLAFHQFYI

SEQ ID No: 7

MVGEEKMSLRNRLSKSRENPEEDEDQRNPAKESLETPSNGRIDIKQLIAKKIKLTAEAEA  
 RLKPFFMKEVGSHFDDFTNLIEKSASLDNGGCALTFSVLEGEKNNHRAKDLRAPPEQ  
 GKIFIARRSLLDELLEVVDHIRTIYHMFIALLILFILSTLVVDYIDEGRVLEFSLLSYAFGKFPT  
 VVWTWWIMFLSTFSVPYFLFQHWATGYSKSSHPLIRSLFHGFLFMIFQIGVLGFGPTYV  
 VLAYTLPPASRFIIIFEQIRFVMKAHSFVRENVPRLNSAKEKSSTVPIPTVNQYLYFLFAP  
 TLIYRDSYPRNPTVRWGYVAMKFAQVFGCFFYVYYIFERLCAPLFRNIKQEPMFSARVLVL  
 CVFNSILPGVLILFLTFFAFLHCWLNAFAEMLRGDRMFYKDWWNSTSYSNYRTWNV  
 VVHDWLYYYAYKDFLWFFSKRFKSAAMLAVFAVSADVHEYALAVCLSFFYPVLFVLFMF  
 FGMAFNIVNDSRKPKIWNVLMWTSFLGNGVLLCFYSQEWEYARQHCPLKNPTFLDYV  
 RPRSWTCRYVF

SEQ ID No: 8

MVKVTFNSALAQKEAKKDEPKSGEEALIIPPDAAVDCKDPDDVVPGQRRAWCWCM  
 CFGLAGVILGGAYLYKYFALQPDDVYYCGIKYIKDDVILNEPSADAPAALYQTIEEN  
 IKIFEEEVEFISVPVPEFADSDPANIVHDFNKKLTAYLDLNLDKCYVPLNTSIVMPRN  
 LELLINIKAGTYLPQSYLIHEHMVITDRIENIDHLGFFIYRLCHDKETYKLQRRETIKGQKR  
 EASNCFAIRHFENKFAVETLICS

SEQ ID No: 9

MLRRPAPALAPAARLLLAGLLCGGGVWAARVNKHKPWLEPTYHGIVTENDNTVLLDPP  
 LIALDKDAPLRFAGEICGFKIHGQNVPFDAVVVDKSTGEGVIRSKEKLDCELQKDYSFTIQ  
 AYDCGKGPDGTNVKKSHKATVHIQVNDVNEYAPVFKEKSYKATVIEGKQYDSILRVEAV  
 DADCSPQFSQICSYEIITPDVPFTVDKDGYIKNTEKLYNGKEHQYKLTVTAYDCGKKRAT  
 EDVLVKISIKPTCTPGWQGWNNRIEYEPGTGALAVFPNIHLETCDEPVASVQATVELETS  
 HIGKGCDRDTYSEKSLHRLCGAAAGTAELLPSPSGSLNWTMGLPTDNGHDSDQVFEF  
 NGTQAVERIPDGVVSVSPKEPFTISVWMRHPGRKKETILCSSDKTDMNRRHHYSLYVH  
 GCRLIFLFRQDPSEEKKYRPAEFHWKLNQVCDEEWHHYVLNVEFPSVTLYADGTSHEP  
 FSVTEDYPLHPSKIETQLVVGACWQEFSGVENDNETEPVTACAGGDLHMTQFFRGNL  
 AGLTLRSGKLADKKVIDCLYTCKEGLDLQVLEDSGRGVQIQAHRSQLVLTLEGEDLGEL  
 DKAMQHISYLSRQFPTPGIRRLKITSTIKCFNEATCISVPPVDGYVMVLQPEEPKISLSG  
 VHHFARAASEFESSEGVLFPRLIISTITREVEPEGDGAEDPTVQESLVSEEIVHLDTC  
 EVTVEGEELNHEQESLEVDMARLQQKGIEVSSSELGMTFTGVDTMASYEEVLHLLRYR  
 NWHARSLLDRKFKICSELNGRYISNEFKVEVNVIAHTANPMEHANHMAAQPQFVHPEH

RSFVDLSGHNLANPHPFAVVHSTATVVIVVCVSSLVFMII LGVFRIRAAHRRTMRDQDTG  
 KENEMDWDDSALTITVNPMETYEDQHSSEEEEEEESEDGEEDDITSAESESSE  
 EEEGEQGDQPQNATRQQQLEWDDSTLSY

SEQ ID No: 10

MSFLIDSSIMITSQLFFFGFWLFFMRQLFKDYEIRQYVVQVIFSVTFAFSCTMFELIIFEIL  
 GVLNSSSRYFHWMNLCVILLILVFMVPFYIGYFIVSNIRLLHKQRLLFSCLLWLTMYFF  
 WKLGDPPILSPKHGILSIEQLISRVGVIGVTLMALLSGFGAVNCPTYMSYFLRNVTDTD  
 ILALERRLLQTMDMIISKKRMAARRTMFQKGEVHNKPSGFWMIKSVTSASGSENL  
 TLIQQEVDALEELSRLFLETADLYATKERIEYSKTFKGKYFNFLGYFFSIYCVWKIFMATI  
 NIVFDRVGVKTDPVTRGIEITVNYLGIQFDVKFWSQHISFILVGIIIVTSIRGLLITLKFFYAIIS  
 SSKSSNVIVLLAQMIMGMYFVSSVLLIRMSMPLYRTIITEVLGELQFNFYHRWFVDVIFLVS  
 ALSSILFLYLAHKQAPEKQMAP

SEQ ID No: 11

MASGRDERPPWRLGRLLLLMCLLLGSSARAHHKAETTTTSAGAEAAEGQFDRY  
 YHEEELESALREAAAAGLPGLARLFSIGRSVEGRPLWVRLTAGLGS LIPEGDAGPDAAG  
 GPDAAGPLLPGRPQVKLVGNMHGDETVSRQVLIYLAAGYRRGDPRLVRLNTTD  
 VYLLPSLNPDGFERA REGDCGFDGGPSGASGRDNSRGDRDLNRSPDQFSTGEPPAL  
 DEVPEVRALIEWIRRNFVLSGNLHGGSVVASYPFDDSPEHKATGIYSKTSDDDEVFKYL  
 AKAYASNHPIMKTGEPHCPGDEDETFKDGITNGAHWDVEGGMQDYNVWANCFEIT  
 LELESCCKYPPASQLRQEENNRESLITLIEKVHIGVKGFVKDSITGSGLENATISVAGINH  
 NITTGRFGDFYRLLVPGTYNLTVVLGYMPLTVTNVVKEGPATEVDFSLRPTVTSVIPD  
 TTEAVSTASTVAIPNILSGTSSSYQPIQPKDFHHHFPMDEIFLRRFANEYPNITRLYSLG  
 KSVESRELYVMEISDNPGVHEPGEPEFKYIGNMHGNEVVGRELLNLIEYLCKNFGTDP  
 EVTDLVHNTRIHLMPSMNPDGYEKSQEGDSISVIGRNNNSNNFDLNRNFQFVQITDPT  
 QPETIAVMSWMKSYPFVLSANLHGGSLVVNYPFDDDEQGLATYSKSPDDAVFQQIALS  
 YSKENSQMFQGRPCKNMYPNEYFPHGITNGASWYNVPGGMQDWNYLQTNCFEVTEL  
 GCVKYPLEKELPNFWEQNRRSLIQFMKQVHQGVRGFVLDATDGRGILNATISVAEINHP  
 VTTYKTGDYWRLLVPGTYKITASARGYNPVTKNVTVKSEGAIQVNFTLVRSSSTDNNES  
 KKGKGASSSTNDASVPTTKEFETLIKDLSAENGLESMLRSSNLALALYRYHSYKDLSE  
 FLRGLVMNYPHITNLNLGQSTEYRHIWSLEISNKPNVSEPEEPKIRFVAGIHGNAPVGT  
 ELLLALAELCLNYKKNPAVTQLVDRTRIVVPSLNPDGRERAQEKDCTSFIGQTNARGK  
 DLDDFTNNASQPETKAIENLIQKQDFSLVALDGGSMLVTYPYDKPVQTVENKETLK

LASLYANNHPSMHMGQPSCPNSDENIPGGVMRGAEWHSHLGSMKDYSVTYGHCP  
 ETVYTSCCYFPSAARLPSLWADNKRSLLSMLVEVHKGVHGFVKDKTGKPISKAVIVLNEG  
 IKVQTKEGGYFHVLLAPGVHNIIIAIDGYQQQHSQVFVHHDAASSVVIVFDTDNRIFGLPR  
 ELVVTVSGATMSALILTACIWCICSIKSNRHKDGFHRLRQHHDEYEDEIRMMSTGSKKS  
 LLSHEFQDETDEEETLYSSKH

SEQ ID No: 12

MTATEALLRVLLLLLAFGHSTYGAECFPACNPQNGFCEDDNVCRCQPGWQGPLCDQC  
 VTSPGCLHGLCGEPGQCICTDGWDGECLCDRVACSSAPCANNGTCVSLDGGLYECS  
 CAPGYSRKDCQKKDGPCVINGSPCQHGGTCVDDEGRASHASCLCPPGFSGNFCEIVA  
 NSCTPNPCENDGVCTDIGGDFRCRCPAGFIDKTCSRPVNCASSPCQNGGTCLQHTQ  
 GQAICFTILGVLTSLVVLGTVGIVFLNKETWVSNLRYNHMLRKKKNLLLQYNSGEDLAV  
 NIIIFPEKIDMTTFSKEAGDEEI

SEQ ID No: 13

MLGLLVALLALGLAVFALLDVWYLVRLPCAVLRARLLQPRVRDLLEQRFPGRVLPSDL  
 DLLLMNNNARYLREADFARVAHLTRCGVLGALRELRAHTVLAASCARHRRSLRLLEPFE  
 VRTRLLGWDDRAFYLEARFVSLRDGFVCALLRFRQHLLGTSPERVVQHLCQRRVEPPE  
 LPADLQHWISYNEASSQLLRMESGLSDVTKDQ

SEQ ID No: 14

MGPGRPAPAPWPRHLLRCVLLGCLHLGRPGAPGDAALPEPNVFLIFSHGLQGCLEAQ  
 GGQVRVTPACNTSLPAQRWKWVSRNRLFNLGTMQCLGTGWPGTNNTASLGMYECDR  
 EALNLRWHCRTLGDQLSLLGARTSNISKPGTLERGDQTRSGQWRIYGSEEDLCALPY  
 HEVYTIQGNSHGKPCTIPFKYDNQWFHGCTSTGREDGHLWCATTQDYGKDERWGFC  
 PIKSNDCETFWDKDQLTDSCYQFNQSTLSWREAWASCEQQGADLLSITEIHEQTYING  
 LLTGYSSTLWIGLNDLDTSGGWQWSDNSPLKYLNWESDQPDNPSEENCGVIRTESSG  
 GWQNRDCSIALPYVCKKKPNATAEPTPPDRWANVKVECEPSWQPFQGHCYRLQAEK  
 RSWQESKKACLRGGGDLVSIHSMAELEFITKQIKQEVEELWIGLNDLKLQMNFEWSDG  
 SLVSFTHWHPFEPNNFRDSLEDCVTIWGPEGRWNDSPCNQSLPSICKAGQLSQGAA  
 EEDHGCRKGWTWHSPSCYWLGEDQVTYSEARRLCTDHGSQLVTITNRFEQAFVSSLI  
 YNWEGEYFWTALQDLNSTGSFFWLSGDEVMYTHWNRDQPGYSRGCVVALATGSAM  
 GLWEVKNCTSFRARYICRQSLGTPVTPELPGPDPTPSLTGSCPQGWASDTKLRYCYKV  
 FSSERLQDKKSWVQAQGACQELGAQLLSLASYEEEHFVANMLNKIFGESEPEIHEQHW

FWIGLNRRDPRGGQSWRSDGVGFSYHNFDRSRHDDDIRGCAVLDLASLQWVAMQ  
 CDTQLDWICKIPRGTDVREPDDSPQGRREWLRFQEAEYKFFEHSTWAQAQRICWTW  
 QAE LTSVHSQAELDFLSHNLQKFSRAQEQQHWIWGLHTSESDGRFRWTGSIINFISWA  
 PGKPRPVGDKKCVYMTASREDWDGDQRCLTALPYICKRSNVTKETQPPDLPTTALGG  
 CPSDWIQLNKCFQVQGQEPQSRVKWSEAQFSCEQQEAQLVTITNPLEQAFITASLPN  
 VTFDLWIGLHASQRDFQWVEQEPLMYANWAPGEPSGPSPAPSGNKPSCAVVLHSPS  
 AHFTGRWDDRSCTEETHGFICQKGTDPSLSPSPAALPPAPGTESYLNFTFRLLQKPLR  
 WHDALLLCESHNASLAYVPDPYTQAFLTQAARGLRTPLWIGLAGEEGSRRYSWVSEEP  
 LNYVGWQDGEPQQPGGCTYVDVDAWRRTSCDTKLQGAVCGVSSGPPPPRISYHG  
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 HLQS YEGQSRGAWLGMNFNPKGTLVWQDNTAVNYSNWGPPGLGPSMLSHNSCYW  
 IQSNSGLWRPGACTNITMGVVCKLPRAEQSSFSPSALPENPAALVVVLMAVLLLALLTA  
 ALILYRRRQSIERGAFEGARYSRSSSSPTEATEKNILVSDMEMNEQQE

SEQ ID No: 15

MNNHVSSKPSTMKLKHTINPIILYFIHFLISLYTILTYIPFYFFSERQEKSNRKAKPVNSK  
 PDSAYRSVNSLDGLASVLYPGCDTLKVF TYAKNKFKNKRLLGTREVLNEEDEVQPNG  
 KIFKKVILGQYNWLSYEDVFVRAFNFGNGLQMLGQKPKTNIAFCETRAEWMIAAQACF  
 MYNFQLVTLYATLGGPAIVHALNETEVNTNIITSKELLQTKLKDIVSLVPRLRHIITVDGKPPT  
 WSDFPKGIIVHTMAAVEALGAKASMENQPHSKPLPSDIAVIMYTSGSTGLPKGMISHS  
 NIIAGITGMAERIPELGEEDVYIGYLPLAHVLELSAELVCLSHGCRIGYSSPQTLADQSSKI  
 KKGSKGDTSMKPTLMAAVPEIMDRIYKNVMNKVSEMSSFQRNLFILAYNYKMEQISKG  
 RNTPLCDSFVFRKVRSLLGGNIRLLCGGAPLSATTQRFMNICFCCPVGQGYGLTESAG  
 AGTISEVWDYNTGRVGAPLVCCIEIKLNWEEGGYFNTDKPHPRGEILIGGQSVTMGYY  
 KNEAKTKADFSEDENGQRWLCTGDIGEFEPDGCLKIIDRKKDVLVKLQAGEYVSLGKVEA  
 ALKNLPLVDNICAYANSYHSYVIGFVVPNQKELTELARKKGLKGTWEELCNSCEMENEV  
 LKVLSEAAIASLEKFEIPVKIRLSPEPWTPETGLVTDAFKLKRKELKTHYQADIEMYGR  
 K

SEQ ID No: 16

MSRLGALGGARAGLGLLLGTAAGLGFLCLLYSQRWKRTQRHGRSQSLPNSDLYTQTS  
 DPGRHVMLLRAVPGGAGDASVPLSLPREGQEKVLDRLDFVLTSLVALRREVEELRSSL  
 RGLAGEIVGEVRCHMEENQRVARRRRFPFVRERSDSTGSSSVYFTASSGATFTDAESE  
 GGYTTANAESDNERDSDKESEDGEDEVSCETVKMGRKDSLDEEEAASGASSALEAG

GSSGLEDPPLLQQADELHRGDEQGKREGFQLLNNKLVYGSRQDFLWRLARAYSDM  
 CELTEEVSEKKSYALDGKEEAEAALEKGDESADCHLWYAVLCGQLAEHESIQRIQSGF  
 SFKEHVDKAIALQPENPMAHFLLGRWCYQVSHLSWLEKKTATALLESPLSATVEDALQS  
 FLKAEELQPGFSKAGRYYISKCYRELGKNSEARWWMKLALELPDVTKEDLAIQKDLEEL  
 EVILRD

SEQ ID No: 17

MVKISFQPAVAGIKGDKADKASASAPAPASATEILLTPAREEQPPQHRSKRGGSVGGVC  
 YLSMGMVVLLMGLVFASVYIYRYFFLAQLARDNFFRCGVLYEDSLSSQVRTQMELEED  
 VKIYLDENYERINVVPVPQFGGGDPADIHDQRGLTAYHDISLDKCYIELNTIVLPPRNF  
 WELLMNVKRGTYLPQTYIIQEEMVVTEHVSDEALGSFIYHLCNGKDTYRLRRRATRRR  
 INKRGAKNCNAIRHFENTFVGETLICGVV

SEQ ID No: 18

MSDKMSSFLHIGDICSPLYAEGSTNGFISTLGLVDDRCVVQPETGDLNNPPKKFRDCLFK  
 LCPMNRYSAQKQFWKAAPGANSTTDAVLNKLHHAADLEKKQNETENRKLLGTVIQY  
 GNVIQLLHLKSNKYLTVNKRLPALLEKNAMRVTLDEAGNEGWSFYIQPFYKLRSIGDSVV  
 IGDKVVLNPVNAGQPLHASSHQLVDNPGCNEVNSVNCNTSWKIVLFMKWSDNKDDILK  
 GGDVVRFLHAEQEKFHTCDEHRKKQHVFLRTTGRQSATSATSSKALWEVEVVQHDPC  
 RGGAGYWNSLFRFKHLATGHYLAEVDPDFEEECLFQPSVDPDQDASRSRLRNAQE  
 KMVYSLVSVPEGNDISSIFELDPTTLRGGDSLVRNSYVRLRHLCTNTWHSTNIPIDKE  
 EEKPVMLKIGTSPVKEDKEAFAIVPVSPAVERDLDFANDASKVLGSIAGKLEKGTTQNE  
 RRSVTKLLEDLVYFVTGGTNSGQDVLEVVFSPKRERQKLMREQNILKQIFKLLQAPFT  
 DCGDGPMRLLEELGDQRHAPFRHICRLCYRVLHSQQDYRKQNQEYIAKQFGFMQKQI  
 GYDVLAEDETTALLHNNRKLEKHITAAEIDTFVSLVRKNREPRFLDYLSDLCVSMNKSIP  
 VTQELICKAVLNPTNADILIETKLVLSRFEFEGVSSTGENALEAGEDEEEVWLFWRDSNK  
 EIRSKSVRELAQDAKEGQKEDRDVLSYRYQLNLARMCLDRQYLAINEISGQLDVDLIL  
 RCMSDENLPYDLRASFTRLHMHVDRDPQEVTVPVKYARLWSEIPSEIAIDDYDSSG  
 ASKDEIKERFAQTMEFVEEYLRDVVCQRFPFSDKEKNKLTFEVVNLARNLIYFGFYNF  
 DLLRLTKILLAILDCVHVTIPISKMAKGEENGNNDVEKLSSNVMRSHGVGELMTQV  
 VLRGGGFLPMTPMAAAPEGNVKQAEPEKEDIMVMDTKLIIIEILQFILNRDYLISCLCI  
 FKREFDESNSQTSETSSGNSSQEGPSNPGALDFEHIEEQAEGIFGGRKVFHEENTP  
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 VCTEGKNVYTEIKCNSLLPL  
 DDIVRVVTHEDCIPEVKIAYINFLNHCYVDTEVEMKEIYTSNHMWKLFENFLVDICRACNN  
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 LMPSQKASVESCI  
 RVLSDVAKSRAIAIPV  
 DLD  
 SQVNNFLKSHSIVQKTAMNWRLSARNA  
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 DVLHRPELLFPENTDAR  
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 TVVNTSDL  
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 QITEEV  
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 READPDDHY  
 QPGETQATADKA  
 KDDLEMSAVITIMQ  
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SEQ ID No: 19

MKDGSRRPQPGPRGAGGRRLASRACARCRGPD  
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LEDYYVSKSAVVFGGFYLFFFTEKILKILLKQKNEHHGHSHYASESLPSKKDQEEGVM  
EKLQNQGDLDHMIPQHCSSELDGKAPMVDEKVIVGSLSVQDLQASQSACYWLKGVRYS  
DIGTLAWMITLSDGLHNFIDGLAIGASFTVSFQGISTSVAILCEEFPHELGDFVILLNAGM  
SIQQALFFNFLSACCCYLGLAGFILAGSHFSANWIFALAGGMFLYISLADMPEMNEVCQ  
EDERKGSILIPFIIQNLGLLTGFTIMVVLTMYSQQIQCIG

SEQ ID No: 20

EPCALTPGPSHLALTFLPSKPGARPQPEGASWDAGPGGAPSADPGEGGPSPMLP  
EGLSSQALSTEAPLPATLEPRIVMGEETCQALLSPRAARTALRDQEGGHASPDPPPELC  
SQGDLSPVSPPPPDSFTPPSTPTKTYALLPACGPHGDARDSEAE LRDELLDSP PAS  
PSGSYITADGDSWASSPSCSLSLLAPAEGLDFPSGWGLSPQGS MVDERELHPAGTPE  
PPSSESSL SADSSSWGQEGHFFDLDFLANDPMIPAALLPFQGS LIFQVEA VEV TPL SP  
EEEEEEAVADPD PGGLAGEGEEDSTSASF LQSLSDLSITE GMDEAF AFR DDT SAASS  
DSDSASYAE ADDERLYSGE PHAQATLL QDSVQ KTEE ESGGAK GLQA QDG TV SWAVE  
AAPQTSDRGAYLSQRQELISEVTE EGLALGQESTATVTPHTLQVAPGLQVEVATRVTPQ  
AGEEETD STAGQESAAMAMPQPSQEGISEILGQESVTAEKLPTPQEETSLTCPDSPQ  
NLKEEGGLDLPGRKPVAAATIVPRQAKEDLTPQDSAMTPPLPLQDTDLSSAPKPVAA  
ATIVSQQAEEGLTLPQDSVMTPPLPLQDTTELSSAPKPVAAATLVSQQAEEGLTLPQDSA  
MTPPLPLQDTDLSSAPKPVAAATLVSQQAEEGLTLPQDSAMTPPLPLQDTDLSSAPKPV  
AAATLVSQQAEEGLTLPQDSAMTPPLPLQDTDLSSAPKPVAAATIVSQQAEEGLTLPQD  
SAMTPPLPLQDTDLSSAPKPVAAATIVSQQAEEGLTLPQDSAMTPPLPLQDTDLSSAPKP  
PVAAATPV SQQAEEGLTLPQDSAMTPPLPLQDTDLSSAPKPVAAATPV SQQAEEGLT  
PQDSAMTAPLPLQDTGPTSGPEPLAVATPQTLQAEAGCAPGTEPVATMAQQEVGEAL  
GPRPAPEEKNAALPTVPEPAALDQVQQDDPQAAEAGTPWAAQEDADSTLGMEALSL  
PEPASGAGEEIAEALSRPGREACLEARAHTGDGAKPDSPQKETLEVENQQEGGLKLLA  
QEHGPRSALGGAREVPDAPP AACPEV SQARLL SPAREER GLSGKSTPEPTLPSAVATE  
ASLDSCPESSVGAVSSLDRGCPDAPAPTSAPTSQQPEPV LGGSVEQPHEVPSVLGTP  
LLQP PENLA KGQP STPV DRPLG PDPSAP GTLAGA ALP PLEPPAPCLCQDPQEDS VEDE  
EPPGSLGLPPPQAGVQPA AA AVSGTT QPLGTGPRVSLSPHSPLLSPKVASMDAKDLAL  
QILPPCQVPPPSGPQSPAGPQGLSAPEQQEDED SLEEDSPRALGSGQHSDSHGESSA  
ELDEQDILAPQTVQCPAQAPAGGSEETIAKAKQSRSEKKARKAMSKLGLRQIQGVTRITI  
QKSKNILFVIAKPDVFKSPASD TYVFGEAKIEDLSQQVHKAAA EKF KVPS EPS AL VPES  
APRPRVRLECKEEEEEE EVDEAGLELRDIELVMAQANVSRAKAVRAL RDNHSDIVNA  
IME LT M

SEQ ID No: 21

PLCPALCPTSPPLPLLPPSVSPPGCLTLWSLSFLFSVPSAPYPHLKTTMATIPDWKLQL  
 LARRRQEEASVRGREKAERERLSQLPAWKRGLLERRRAKLGSPGEPSPVLGTVEAG  
 PPDPEAVLLEAIGPVHQNRFIRQERQQQQQQQRSEELLAERKPGPLEARERRPSP  
 GEMRDQSPKGRESREERLSPRETRERRLGIGGAQELSLRPLEARDWRQSPGEVGDRS  
 SRLSEAWKWRLSPGETPERSLRLAESREQSPRRKEVESRLSPGESAYQKLGLTEAHK  
 WRPDSRESQEQLVQLEATEWRLRSGEERQDYSEECGRKEEWPVPGVAPKETAELS  
 ETLTREAQGNSSAGVEAAEQRPVEDGERGMKPTEGWKWTNSGKAREWTPRDIEAQ  
 TQKPEPPESAEKLLESPGVEAGEGEAEKEEAGAQGRPLRALQNCCSVPSPLPPEDAGT  
 GGLRQQEEEAVELQPPPPAPLSPPPPAPTAPQPPGDPLMSRLFYGVKAGPGVGAPRR  
 SGHTFTVNPRRSVPPATPATPTSPATVDAAVPGAGKKRYPTAAEELVLGGYLRLSRSC  
 AKGSPERHHKQLKISFSETALETTYQYPSESSVLEELGPEPEVPSAPNPPAAQPDDEED  
 EEELLLQPELQGGLRTKALIVDESCRR

SEQ ID No: 22

LQLSVKMSVLISQSVINYVEEENIPALKALLEKCKDUDERNECGQTPLMIAAEQGNLEIVK  
 ELIKNGANCNLEDLDNWTLISASKEGHVHIVEELLKCGVNLEHRDMGGWTALMWACY  
 KGRTDVVELLSHGANGPSVTGLYSVPIIWAAGRGHADIVHLLLQNGAKVNCSDKYGTT  
 PLVWAARKGHLECVKHLLAMGADVQEGANSMTALIVAVKGGYTQSVKEILKRNPNVN  
 LTDKDGNNTALMIASKEGHTEVQDLDAGTYVNIPDRSGDTVLIGAVRGGHVEIVRALLQ  
 KYADIDIRGQDNKTALYWAVEKGNATMVRDILQCNPDTEICTKDGETPLIKATKMRNIEV  
 VELLDKGAKVSAVDKKGDTPLHIAIRGRSRKLAELLRNPKDGRLLYRPNKAGETPYNI  
 DCSHQKSILTQIFGARHLSPTETDGDMGYDLYSSALADILSEPTMQPPICVGLYAQWG  
 SGKSFLKKLEDEMKTFAQQQIEPLFQFSWLIVFLLLCGGLGLLFAFTVHPNLGIAVSL  
 SFLALLYIFFIVIYFGGRREGESWNWAWVLSTRALARHIGYLELLLKLMFVNPPPEQTTK  
 ALPVRFLFTDYNRLSSVGGGETSLAEMIATLSDACEREFGFLATRLFRVFKTEDTQGKKK  
 WKKTCCLPSFVIFLFIIGCIISGITLLAIFRVDPKHLTVNAVLISIASVVGAFVLCRTWWQ  
 VLDSSLNSQRKRLHNAASKLHKLKSEGFMKVLKCEVELMARMAKTIDSFTQNQTRLVVII  
 DGLDACEQDKVLQMLDTVRLFSKGPFIAIFASDPHIICKAINQNLNSVLRDSNINGHDYM  
 RNIVHLPVFLNSRGLSNARKFLVTSATNGDVPSCSDTTGIQEDADRRVSQNSLGEMTKLG  
 SKTALNRRDTYRRRQMQRITRQMSFDLTKLVTEDWFSDISPQTMRRLLNIVSVTGR  
 LRANQISFNWDRLASWINLTEQWPYRTSWLILYLEETEGIPDQMTLKIYERISKNIPTTK  
 DVEPLLEIDGDIRNFEVFLSSRTPVLVARDVKVFLPCTVNLDPKLREIIADVRAAREQISIG

GLAYPPLPLHEGPPRAPSGYSQPPSVCSSTSFGPFAGGVSPQPHSSYYSGMTGPQ  
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 DSSRGSGPAPGPVVLNSLNVDAVCEKLKQIEGLDQSMLPQYCTTIKKANINGRVLAQC  
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 GSIHSNLEQEKGKDSEPKPDDGRKSFLMKRGDVIDYSSSGVSTNDASPLDPITEEDEKS  
 DQSGSKLLPGKKSSERSSLFQTDLKLKGSLRYQKLPSDEDESGTEESDNTPLKDDK  
 DRKAEGKVERVPKSPEHSAEPIRTFIKAKEYLSDALLDKDSSDSGVRSSESSPNHSLH  
 NEVADDSQLEKANLIELEDDSHSGKRGIPHSLSGLQDPIIARMSICSEDKKSPSECSLIAS  
 SPEENWPACQKAYNLN RTPSTVTLNNSAPANRANQNFDEMEGIRETSQVILRPSSSP  
 NPTTIQNENLKSMTHKRSQRSSYTRLSKDPPFHAAASSESTGFGEERESIL

SEQ ID No: 23

MDLEGDRNGGAKKKNNFKLNNKSEKDKKEKKPTVSFSMFRYSNWLDKLYMVVGTLA  
 AIIHGAGLPLMMLVFGEMTDIFANAGNLEDLMSNITNRSDINDTGMNLEEDMTRYAYY  
 YSGIGAGVLVAAYIQSFVCLAAGRQIHKIRKQFFHAIMRQEIGWFDVHDVGELNTRLTD  
 DVSKINEGIGDKIGMFFQSMATFFTGFIVGFTRGWKLTVILAISPVLGLSAAVWAKILSSF  
 TDKELLAYAKAGAVAEEVLAIRTVIAFGGQKKELERYNKNLEEAKRIGIKKAITANISIGA  
 AFLLIYASYALAFWYGTTLVLSGEYSIGQVLTFFSVLIGAFSVGQASPSIEAFANARGAA  
 YEIFKIIDNKPSIDSYSKSGHKPDNIKGNLEFRNVHFSYPSRKEVKILKGLNLKVQSGQTV  
 ALVGNSGCGKSTTVQLMQRLYDPTEGMVSVDGQDIRTINVRFLREIIGVVSQEPVLFAT  
 TIAENIRYGRENTMDEIEKAVKEANAYDFIMKLPHKFDTLVGERGAQLSGGQKQRIAIA  
 RALVRNPKILLDEATSALDTESEAVVQVALDKARKGRTTIVIAHRLSTVRNADVIAGFDD  
 GVIVEKGNHDELMKEGIYFKLVTMQTAGNEVELENAADESKSEIDALEMSSNDSRSSLI  
 RKRSTRRSVRGSQAQDRKLSTKEALDESIPPVSFWRIMKLNLTEWPYFVVGVFCAIING  
 GLQPAFAIIFSKIIGVFTRIDDPETKRQNSNLFSLLFLALGIISFITFFLQGFTFGKAGEILTK  
 RLRYMVFRSMLRQDVSWFDDPKNTTGALTTRLANDAAQVKGAIGSRLAVITQNIANLGT  
 GIISFIYGWQLLLLLAIVPIIAIGVVEMKMLSGQALKDKKELEGAGKIAAEAIENFRTVVS  
 LTQEQQKFEHMYAQSLQVPRNSLRKAHIFGITFSFTQAMMYFSYAGCFRGAYLVAHKL  
 MSFEDVLLVFSAVVFGAMA VGQVSSFAPDYAKAKISAHHIIMIIKTPLIDSSTEGLMPN  
 TLEGNVTGEVVFNYPTRPDIPVLQGLSLEVKKGQTLALVGSSGCGKSTVVQLLERFYD  
 PLAGKVLLDGKEIKRLNVQWLRAHLGIVSQEPILFDCSIAENIAYGDNSRVVSQEEVRAA  
 KEANIHA FIESLPNKYSTKVGDKGTQLSGGQKQRIAIA RALVRQPHILLDEATSALDTE

EKVVQEALDKAREGRTCIVIAHRLSTIQNADLIVVFQNGRVKEHGTHQQLLAQKGIYFSM  
VSVQAGTKRQ

SEQ ID No: 24

MTLARFVLALMLGALPEVVGFDVLNDLHHSHRHSPAGPHYPYLLPTQQRPPRTRP  
PPPLPRFPRPPRALPAQRPHALQAGHTPRPHPWGCPAGEPWVSVTDFGAPCLRWAE  
VPPFLERSPPASWAQLRGQRHNFCRSPDGAGRWCFYGDARGKVDWGYCDCRHGS  
VRLRGKGNEFEGTVEVYASGVWGTVCSSHWDSDASVICHQLQLGGKIAKQTPFSG  
LGLIPIYWSNVRCRGDEENILLCEKDIWQGGVCPQKMAAAVTCSFSHGPTFPIIRLAGGS  
SVHEGRVELYHAGQWGTVCDDQWDDADAEVICRQLGLSGIAKAWHQAYFGEGLSGPV  
MLDEVRCTGNELSIEQCPKSSWGEHNCGHKEDAGVSCTPLTDGVIRLAGGKGSHEGR  
LEVYYRGQWGTVCDDGWTELNTYVVCRQLGFKYGKQASANHFEESTGPIWLDDVSCS  
GKETRFLQCSRRQWGRHDCSHREDVSIACYPGGEGHRLSLGFPVRLMDGENKKEGR  
VEVFINGQWGTICDDGWTDKDAAVICRQLGYKGPARARTMAYFGEKGKPIHVDNVKCT  
GNERSLADCIKQDIGHNCRHSEDAGVICDYFGKKASGNSNKESLSSVCGLRLLHRRQ  
KRIIGGKNSLRGGWPWQVSLRLKSSHGDGRLLCGATLSSCWVLTAACFKRYGNSTR  
SYAVRVGDYHTLVPEEEEEEIGVQQIVIHCYRPDRSDYDIALVRLQGPEEQCARFSSH  
VLPACLPLWRERPQKTASNCFITGWGDTGRAYSRTLQQAAIPLLPKRFCEERYKGRFT  
GRMLCAGNLHEHKRVDSCQGDSGGPLMCERPGESVVYGVTSWGYGCGVKDSPGV  
YTKVSAFVPWIKSVTKL

SEQ ID No: 25

LAVVGFALMTQLFLWEYGDLHLFGPNQRPAWCYDPCEAVLVEPIEGLDFPNASTGN  
PSTSQAWLGLLAGAHSSLIASFYWTLTNNNDHTQEPESAQQGEEVLRQLQTLAPKGVN  
VRIAVSKPSGPQPQADLQALLQSGAQVRMVDMQKLTHGVLHTKFVVVDQTHFYLGS  
NMDWRSLTQVKELGVVMYNCSCLARDLTKIFEAYWFLGQAGSSIPSTWPRFYDTRYN  
QETPMEICLNGTPALAYLASAPPPLCPSGRTPDLKALLNVVDNARSFIYVAVMNYLPTLE  
FSHPHRFWPAIDDGLRRATYERGVKVRLLISCWGHSEPSMRAFLLSLAALRDNHTHS  
QVKLFVVPADEAQARIPIYARVNHNKYMVTERATYIGTSNWSGNYFTETAGTSLVTQN  
GRGGLRSQLEAIFLRDWDSVPYSHDLTSADSGVNACRLL

SEQ ID No: 26

MGAYLSQPNTVKCSGDGVGAPRLPLPYGFSAMQGWRVSMEDAHNCIPELDSETAMFS  
VYDGHGSEEVALYCAKYLPIIKDQKAYKEGKLQKALEDAFLAIDAKLTTEEVKELAQIA

GRPTED EDEKEVADEDVDNEEAALLHEEATMTIEELLTRYGQNCHKGPPHSKSGGG  
 TGEEPGSQGLNGEAGPEDSTRETPSQENGPTAKAYTGFSSNSERGTEAGQVGEPGIP  
 TGEAGPSCSSASDKLPRVAKSKFFEDSEDESDEAEEEEEDSEECEEEEDGYSSEEAEEN  
 EEDEDDEEAEEDDEEEEEEEMVPGMEGKEEPGSDSGTTAVVALIRGKQLIVANAGDS  
 RCVVSEAGKALDMSYDHKPEDEVELARIKNAGGKVMDGRVNGGLNLSRAIGDHFYKR  
 NKNLPPEEQMISALPDIKVLTLDHEFMVIACDGIVNMVMSQEVVDFIQSKISQRDENG  
 ELRLLLSSIVEELLDQCLAPDTSGDGTGCDNMTCIICFKPRNTAELQPESGKRKLEEVLST  
 EGAEENGNSDKKKKAKRD

SEQ ID No: 27

MKFLLDILLPLLLIVCSLESFVKLFIPKRRKSVTGEIVLITGAGHGIGRLTAYEFAKLKSKL  
 VLWDINKHGLEETAAKCKGLGAKVHTFVVDCSNREDIYSSAKVKAEIGDVSILVNNAGV  
 VYTSDLFATQDPQIEKTFEVNVLAHFWTTKAFLPAMTKNNHGHIVTVASAAGHVSVPFLL  
 AYCSSLKFAAVGFHKTLTDELAALQITGVKTTCLCPNFVNTGFIKNPSTSLGPTLEPEEVV  
 NRLMHGILTEQKMIFIPSSIAFLTTLERILPERFLAVLKRKISVKFDAVIGYKMKAQ

SEQ ID No: 28

MGAVARAHGGLRVARARES VAGGRHRGAGRPGARAAGAAAGLVRAEAGGRRAGRG  
 RRPGRGLPTGGGLAAA AVGREVAQGLCDAIRLDGGLDLLRLLQAPELET RVQAARL  
 LEQILVAENRDRVARIGLGVILNLAKERPELARSVAGILEHMFKHSEETCQLVAAGG  
 LDAVLYWCRRTDPA LLRH CALALGN CALHGGQAVQRRMVEKRAAEWL FPLAF SKED E  
 LLRLHACLAVAVLATNKEVEREVERSGTLALVEPLVASLD PGRFARCLVDASDTSQGRG  
 PDDLQRLVPLLD SNRLEAQCIGAFYLCAAAIKSLQGKTFVSDIGAIQSLKRLVSYSTNG  
 TKSALAKRALRLLGEEVPRPILPSVPSWKEAEVQTWLQQIGFSKYCESFREQV DGDLL  
 LRLTEEEELQTDLG MKSGITRK RFFRELTELKT FANYSTCDRSNLADWLGS LDPRFRQYT  
 YGLVSCGLDRSLLHRVSEQQLLED CGIHLGVHRAR ILTAAREMLHSPLPCTGGKPSGDT  
 PDVFISYRRNSGSQ LASLLKVHLQLHGFSV FIDVEKLEAGKFEDKLIQSVMGARNFVLV  
 SPGALDKCMQDH DCKDWV HKEIVT ALSCGKNIVPIIDGF EWPEPQV LPEDMQAVLTFN  
 GIKWSHEYQEATIEKIIRFLQGRSS RDSSAGSDTSLEGAAPMGPT

SEQ ID No: 29

MSGELPPNINIKEPRWDQSTFIGRANHFFTVDPRNILLTNEQLESARKIVHDYRQGIVP  
 PGLTENELWRAKYIYDSA FHPDTGEKMILIGRMSAQVPMNMTITGCMMTFYRTTPAVLF  
 WQWINQSFnAVVNYTNRSGDAPLT VNELGTAYVSATTGAVATALGLNALT KHV SPLIGR

FVPFAAVAAANCINIPLMRQRELKVGVIPVTDENGRLGESANAAKQAITQVVVSRLMAA  
PGMAIPPFIMNTLEKK AFLKRFPWMSAPIQVGLVGFC LVFATPLCCALFPQKSSMSVTSL  
EAEELQAKIQESHPELRRVYFNKGL

SEQ ID No: 30

MATRSSRRESRLPFLFTLVALLPPGALCEVWTQRLHGGSAPLPQDRGFLVVQGDPREL  
RLWARGDARGASRADEKPLRRKRSAALQPEPIKVYQGVSLNDSHNQMVVHWAGEKS  
NVIVALARDSLALARPKSSDVYVSYDYGKSFKKISDKLNFGLGNRSEAVIAQFYHSPADN  
KRYIFADAYAQYLWITFDFCNTLQGFSIPFRAADLLLHSKASNLLGFDRSHPNKQLWKS  
DDFGQTWIMIQEHVKSFSWGIDPYDKPNTIYIERHEPSGYSTVFRSTDFFQSRENQEVL  
EEVRDFQLRDKYMFAKVVHLLGSEQQSSVQLWVSFGRKPMRAAQFVTRHPINEYYIA  
DASEDQVFVCVSHSNRTNLYISEAEGLKFSLSLENVLYYSPGGAGSDTLVRYFANEPEF  
ADFHRVEGLQGVYIATLINGSMNEENMRSVITFDKGGTWEFLQAPAFTGYGEKINCELS  
QGCSLHLAQRLSQLLNQLRRMPILSKESAPGLIATGSVGKNLASKTNVYISSAGARW  
REALPGPHYYTWGDHGGIITAIAQGMETNELKYSTNEGETWKTIFSEKPVFVYGLTEP  
GEKSTVFTIFGSNKENVHSWLILQVNATDALGPCTENDYKLWSPSDERGNECLLGHK  
TVFKRRTPHATCFNGEDFDRPVVVSNCSTREDYECDFGFKMSEDLSLEVCPDPEFS  
GKSYSPPVPCPGSTYRRTRGYRKISGDTCSGGDVEARLEGELVPCPLAEEENEFLYAV  
RKSIIYRYDLASGATEQLPLTGLRAAVALDFDYEHNCLYWSDLALDVIQRLCLNGSTGQE  
VIINSGLETVEALAFEPLSQLLYWVDAGFKKIEVANPDGDFRLTIVNSSVLDPRRALVLVP  
QEGVMFWTDWGDLKPGIYRSNMDGSAAYHLVSEDVWKWPNGISVDDQWIYWTDAYLE  
CIERITFSGQQRSVILDNLPHPYAIAVFKNEIYWDDWSQLSIFRASKYSGSQMEILANQLT  
GLMDMKIFYKGKNTGSNACVPRPCSLLCLPKANNSRSCRCPEDVSSSVLPSGDLMCD  
CPQGYQLNNNTCVKEENTCLRQNQYRCNSNGNCINSIWWCDFNDGDMSDERNCPPTI  
CDLDTQFRCQESGTCIPLSYKCDLEDDCGDNSDESHCEMHQCRSDEYNCSSGMCIRS  
SWVCDGDNDCRDWSDEANCTAIHTCEASFQCRNGHCIPQRWACDGDTDCQDG  
DEDPVNCEKKCNGFRCPNGTCIPSSKHCDGLRDCSDGSDEQHCEPLCTHFMDFVCKN  
RQQCLFHSMVCDGIQCRDGSDDEAAFAGCSQDPEFHVCDEFGFQCQNGVCISLIWK  
CDGMDDCGDYSDEANCENPTEAPNCSRYFQFRCENGHCIPNRWKCDRENDGDWS  
DEKDCGDSHILPFSTPGPSTCLPNYYRCSSGTCVMDTWVCDGYRDCADGSDEEACPL  
LANVTAASTPTQLGRCDRFEFECHQPKTCIPNWKRCDGHQDCQDGRDEANCPTHSTL  
TCMSREFQCEDGEACIVL SERCDGFLDCSDESDEKACSDELTVYKVQNLQWTADFSG  
DVTLTWMRPKKMPASCVYNVYYRVVGESIWKTLETHSNKNTV LKVLKPDTTYQVKV  
QVQCLSKAHNTNDFVTLRTPEGPDAPRNLQLSLPRAEGVIVGHWAPPIHTHGLIREYI

VEYSRSGSKMWSQRAASNFTIEKNLLVNTLYTVRVAAVTSRGIGNWSDSKSITTIKGK  
 VIPPPDIHDSYGENYLSFTLTMESDIKVNGYVVNLFWAFDTHKQERRTLNFRGSILSHKV  
 GNLTAHTSYEISAWAKTDLGDSPLAFEHVMTRGVRPPAPSLKAKAINQTAECTWTGP  
 RNVVYGYIFYATSFLDLYRNPKSLTSLHNKTIVSKDEQYLFLVRVVVPYQGPSSDYVVV  
 KMIPDSRLPPRHLHVVTGKTSVVIKWESPYDSPDQDLYAIAVKDLIRKTDRSYKVKS  
 NSTVEYTLNKLEPGGKYHIIVQLGNMSKDSSIKITVSLsapDALKIITENDHVLLFWKSLA  
 LKEKFNFESRGYEIHMFDSAMNITAYLGNTTDNFFKISNLKMGHNYTFTVQARCLFGNQI  
 CGEPAILLYDELGSGADASATQAARSTDVAAVVVPILFLILLSLGVGFAILYTKHRRRLQSS  
 FTAFANSHYSSRLGSAIFSSGDDLGEDDEDAPMITGFSDDVPMVIA

SEQ ID No: 31

MLSLDFLDDVRRMNKRQLYYQVLNFGMIVSSALMIWKGLMVITGSESPIVVVLGGSMEP  
 AFHRGDLLFLTNRVEDPIRVGEIVVFRIEGREIPIVHRVLKIHEKQNGHIKFLTKGDNNAVD  
 DRGLYKQGQHWLEKKDVGRARGFVPYIGIVTILMNDYPKFKYAVLFLLGLFVLVHRE

SEQ ID No: 32

MNTVLSRANSLFAFSLSVMAALTFCFITTAFKDRSVPVRLHVSRIMLKNVEDFTGPRER  
 SDLGFIITSITADLENIFDWNVKQLFLYLSAEYSTKNNALNQVVLWDKIVLRGDNPKLLLK  
 DMKTKYFFFDDGNGLKGNRNVTTLSWNVVPNAGILPLVTGSGHVSVPFPDTYEITKSY

SEQ ID No: 33

MAAAAVQGGRSGGGSGCSGAGGASNCGTGSGRSGLDKWKIDDKPVKIDKWDGSAV  
 KNSLDDSakkVllekykyvenfglidgrltictiscffaivaliwdymhpfpeskpvlaLC  
 VISYPLFMLSFMVMMGILTITYSYKEKSIFLVAHRKDPTGMDPDDIWQLSSLKRFDDKYTL  
 KLTFISGRTKQQREAETKSIAKFFDHSGTLVMDAYEPEISRLHDSLAIERKIK

SEQ ID No: 34

MRPEPGGCCCRRTVRANGCVANGEVRNGYVRSSAAAAAAAAGQIHHVTQNGGLYK  
 RPFNEAFEETPMLVAVLTYVGYGVTLFGYLRDFLRYWRIEKCHHATEREEQKDFVSLY  
 QDFENFYTRNLYMRIRDNWNRPICSVPGARVDIMERQSHDYNWSFKYTGNIIKGVINMG  
 SYNYLGFARNTGSCQEAAKVLEEYGAGVCSTRQEIGNLDKHEELEELVARFLGVEAA  
 MAYGMGFATNSMNIPALVGKGCLILSDELNHASLVLGARLSGATIRIFKHNNMQSLEKLL  
 KDAIVYGGQPRTRRPWKKILILVEGIYSMEGSIVRLPEVIALKKKYKAYLYLDEAHSIGALGP  
 TGRGVVEYFGLDPEDVDVMMGTFTKSF GASGGYIGGKKEIDYLRTHS A VYATSL S

PPVVEQIITSMKCIMGQDGTSLGKECVQQLAENTRYFRRRLKEMGFIYGNEDSPVVPL  
MLYMPAKIGAFGREMLKRNIGVVVVGFPATPIIESRARFCLSAHTKEILDTALKIDEVG  
DLLQLKYSRHLRVPLLDRPDETTYEETED

SEQ ID No: 35

MPAHLLQDDISSYTTTTITAPPSRVLQNGGDKLETMPLYLEDDIRPDIKDDIYDPTYKD  
KEGPSPKVEYVWRNIILMSLLHLGALYGITLIPTCKFYTWLGVFYYFVSALGITAGHRL  
WSHRSYKARLPLRLFLIIANTMAFQNDVYEWARDHRAHHKFSETHADPHNSRRGFFFS  
HVGWLLVRKHPAVKEKGSTLDSLDEAEKLVMFQRRYYKPGLLMMCFILPTLVPWYFW  
GETFQNSVFVATFLRYAVVLANATLVNSAAHLFGYRPYDKNISPENILVSLGAVGEGF  
HNYHHSFPYDYSASEYRWHINFTFFFIDCMAALGLAYDRKKVSKAILARIKRTGDGNYK  
SG

SEQ ID No: 36

MSGLSGPPARRGPFPALLLFLLGPRVLVAISFHLPINSRKCLREEIHKDLLVTGAYEISD  
QSGGAGGLRSHLKIDTSAGHILYSKEDATKGKFAFTTEDYDMFEVCFESKGTGRIPDQL  
VILDMKHGVEAKNYEEIAKVEKLKPLEVELRRLEDLSESIVNDFAYMKKREEEMRDTNES  
TNTRVLYFSIFSMFCLIGLATWQVFYLRRFFKAKKIE

SEQ ID No: 37

MSGCGLFLRTTAAARACRGLVVSTANRRLLRTSPPVRAFAKELFLGKIKKKEVFPFPEV  
SQDELNEINQFLGPVEKFFTEEVDSRKIDQEGKIPDETLEKLKSLGLFGLQVPEEYGLLG  
FSNTMYSRLGEIISMDGSITVTLAAHQAIKGIILAGTEEQKAKYLPKLASGEHIAFCLT  
EPASGSDAASIRSRTALSEDKKHYILNGSKVWITNGGLANIFTVFAKTEVVDSDGSVKDK  
ITAFIVERDFGGVTNGKPEDKLGIRGSNTCEVHFENTKIPVENILGEVGDGFKVAMNILNS  
GRFSMGSVVAGLLKRLIEMTAEYACTRKQFNKRLSEFGLIQEKFALMAQKAYVMESMT  
YLTAGMLDQPGFPDCSIEAAMVKVFSSEAWQCVSEVLQILGGLGYTRDYPYERILRDT  
RILLFEGTNEILRMYIALTGLQHAGRILTTRIHELKQAKVSTVMDTVGRRLRDSLGRVVDL  
GLTGNHGVVHPSLADSANKFEENTYCFGRTVETLLLRFGKTIMEQLVLKRVANILINLY  
GMTAVLSRASRSIRIGLRNHDHEVLLANTFCVEAYLQNLFSLSQLDKYAPENLDEQIKKV  
SQQILEKRAYICAHPLDRTC

SEQ ID No: 38

MFSLSSTVQPQVTVPPLSHLINAFTPKNTSVSLSGVSVSQNQHRDVVPEHEAPSSEPSL  
 NLRDLGLSELKIGQIDQLVENLLPGFCKGKNISSHWHTSHVSAQSFFENKYGNLDIFSTL  
 RSSCLYRHHSRALQSICSDLQYWPFIQSRGFKTLKSRTTQLQSTSERLAETQNIAPSF  
 VKGFLLRDRGSDVESLDKLMKTKNIEAHQDAFKTGFAEGFLKAQALTQKTNDSLRRTR  
 LILFVLLLFGIYGLLKNPFLSVRFRTTGLDSAVDPVQMKNVTFEHVKGVEEAKQELQEVE  
 VEFLKNPQKFTILGGKLPKGILLVGPPGTGKTLARAVAGEADVPFYASGSEFDEMVF  
 GVGASRIRNLREAKANAPCVIFIDELEDSVGGKRIESPMHPYSRQTINQLLAEMDGFKPN  
 EGVIIIGATNFPEALDNALIRPGRFDMQTVPRPDVKGRTEILKWYLNKIKFDQSVDPEIIA  
 RGTVGFGSAAELENLVNQAALKAAVDGKEMVTMKELEFSKDKILMGPERRSVEIDNKNK  
 TITAYHESGHAIAYYTAKDAMPINKATIMPRGPTLGHVSLLPENDRWNETRAQLLAQMDV  
 SMGGRVAEEELIFGTDHITTGASSDFDNATKIAKRMVTKFGMSEKLGVMTYSDTGKLSPE  
 TQSAIEQEIRILLRDSYERAKHILKTHAKEHKNLAEALLTYETLDAKEIQIVLEGKKLEVR

SEQ ID No: 39

MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGEgg  
 GPEPGPANAKWLKEGQNQLRRAATAHRDQRNRNTLTLAEEASQEPEMAPLGPKGHLIH  
 YSELELSAHNAANRGLRGPGLIISTQEQQPDEGEEEKAAAGEAEAAAAEDDDDEEEEDLS  
 SPPGLPEPLESVEAPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
 SYGSPEEDTDSFWNPNAFETDSQDPAGWMRVQDTSGTYWHIPTGTTWEPPGRASP  
 SQGSSPQEESQLWTGFAHGEFGEDGEFWKDEPSDEAPMELGLKEPEEGTLTFPAQS  
 LSPEPLPQEEEKLPPRNTNPGIKCFAVRSLGWVEMTEELAPGRSSVAVNNCIRQLSYH  
 KNNLHDPMSSGGWGEKDLLLQLEDETQLVEPQSQALLHAQPIISIRVGVRDSDGRD  
 FAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICSKARPPPLPGLIMAERRNARCLVN  
 GLSLDHSKLVDVPFQVEFPAPKNELVQKFQVYYLGNVPVAKPGVDVINGALESVLSSS  
 SREQWTPSHVSVAPATLTLHQQTAVLGECRVRLSFLAVGRDVHTFAFIMAAGPASF  
 CCHMFWCEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWT  
 VRRGVQSLWGSLKPKRLGAHTP

SEQ ID No: 40

RHTRTHRDTRHHTYTHAHTDAHTCTHMHRDTQMHTHTICRKKYALTNQAAAGLSDPAA  
 QPLLNGNSANIKLVNGENQLRKAEEQGQQDPNKNLSPTAVINITSEKLEGKEPHPQDS  
 SSCEILPSQPRRTKSFLNYYADLETSARELEQNRGNHGTAEEKSQPVQGQASTIIGNG  
 DLLLQKPNRPQSSPEDGQVATVSSPETKKDHPKTGAKTDCALHRIQNLAPSDEESSW  
 TTLSQDSASPSSPDETDIWSDFQTDPLPPGWKRVSAGTYYWHIPTGTTQWERP

VSIPADLQGSRKGSLSVTPSPTPENEKQPWSDFAVLNGGKINSDIWKDLHAATVNPDP  
 SLKEFEGATLRYASLKLRLNAPHPD-DDSCSINSDEAKCFAVRSLGVVEMAEDLAGP  
 KSSVAVNNCIRQLSYCKNDIRDVTGIGEKGKDMYLILENDMLSLVDPMDRSVWHSQPIV  
 SIRVGVGRDNGRDFAYVARDKDTRILKCHVFRCDTPAKAIATSLHEICSKIMAERKNAK  
 ALACSSLQERANVNLDVPLQVDFPTPKTELVQKFHVQYLGMLPVDKPGMDILNSAIEN  
 LMTSSNKEDWLSVNMNVADATVTVISEKNEEEVLVECRVRFLSFMGVGKDVTFAFIM  
 DTGNQRFECHVFWCEPNAGNVSEAVQAACMLRYQKCLVARPPSQVRPPPPPDSV  
 TRRVTTNVKRGVLSIDTLKQKRPTVTEMP

SEQ ID No: 41

MAFVCLAIGCLYTFLISTTFGCTSSSDTEIKVNPPQDFEIVDPGYLGYLYLQWQPPLSLD  
 HFKECTVEYELKYRNIGSETWKTIITKNLHYKDGFDLNKGIEAKIHTLLPWQCTNGSEVQ  
 SSWAETTYWISPQGIPETKVQDMDCVYYNWQYLLCSWKPGIGVLLDTNYNLFYWEGL  
 DHALQCVDYIKADGQNIGCRFPYLEASDYKDFYICVNGSENKPIRSSYFTFQLQNIVKP  
 LPPVYLTFTRESSCEIKLKWSIPLGPIPACRCDYEIEIREDDTTLVTATVENETYTLKTTNE  
 TRQLCFVVRSKVNIYCSDDGIWSEWSDKQCWEGEDLSKKTLLRFWLPFGFILILVIFVTG  
 LLLRKPNTPKMIPEFFCDT

SEQ ID No: 42

MVNYAWAGRSQRKLWWRSVAVLCKSVVRPGYRGGLQARRSTLLKTCARARATAPG  
 AMKMVAPWTRFYSNSCCCLCCHVRTGTILLGVWYLIINAVVLLILLSALADPDQYNFSSSE  
 LGGDfefMDDANMCIAIAISLLMILICAMATYGAYKQRAAWIIPFFCYQIFDFALNMLVAIT  
 VLIYPNSIQEYIRQLPPNFPYRDDVMSVNPTCLVLIILLFISIILTFKGYLISCVWNCYRYING  
 RNSSDVLYVTSNDTTVLLPPYDDATVNGAAKEPPPPYVSA

SEQ ID No: 43

MGSELETAMETLINVFHAGSGKEGDKYKLSKKELKELLQTELSGFLDAQKDVDADVKVM  
 KELDENGDGEVDFQEYVVLVAALTVCNNFFWENS

SEQ ID No: 44

MSELEKAMVALIDVFHQYSGREGDKHKLKKSELKELINNELSHFLEEIKEQEVVVDKVMET  
 LDNDGDGECDFQEFAFVAMVTTACHEFFEHE  
 SEQUENCES OF THE INDIVIDUAL PROTEINS

SEQ ID No: 45

IATVIVITVMLKKKQYTSIHGVVEVDAAVTPEERHLSKMQQQNGYENPTYKFFEQMQN

SEQ ID No: 46

MASALEQFVNSVRQLSAQGQMTQLCELINKSGELLAKNLSHLDTVLGALDVQEHSGLVL  
AVLFVKFSMPSVPDFETLFSQVQLFISTCNGEHIRYATDTFAGLCHQLTNALVERKQPLR  
GIGILKQAIDKMQMNTNQLTSIHADLCQLCLAKCFKPALPYLDVDMMDICKENGAYDAK  
HFLCYYYYGGMIYTGLKNFERALFYEQAITTPAMAVSHIMLESYKKYILVSLILLGKVQQ  
LPKYTSQIVGRFIKPLSNAZHelaqvystnnpseLRNLVNKHSETFTRDNNMGLVKQCL  
SSLYKKNIQRLTKTFLTLSQDMA SRVQLSGPQEA KYVLHMIEDGEIFASINQKDGMVS  
FH DNPEKYN NPAMLHNIDQEMLK CIEL DERLKAMDQEITVNPQFVQKSMGSQEDDSGN  
KPSSYS

SEQ ID No: 47

MSNL SKGT GSR KDT KM RIR AFPM TMDE KYV NSI W DLL KNA I QEI QR KN NS GLS FEEL YR  
NAYTM VL KH GEK LY TGL REV VTEH LINK VRED VLN SLNNN FL QTL NQ AW ND HQ TA MV  
MIRDIL MYMD RVY VQQ NN VENV YNL GLI IF RDQ VV RY GC IR DHL RQ TL L DMIA RER KGEV  
VDRGAIRNACQMLMILGLEGRSVYEEDFEAPFLEMSAEFFQMESQKFLAENSASVYIKK  
VEARINEEIERVVMHCLDKSTEPIVKVVERELISKHMKTIVEMENSGLVHMLKNGKTEDL  
GCMYKLFSRVPNGLKTMCECMSSYLREQKALVSEEGEGKNPVVDYIQGLLDLKSRFDR  
FLLESFNNDRLFKQTIA GD FEYFLN LNSRSPEYLSFIDDKLKKGVKGLTEQEVTILDKA  
MVLFRFMQEKF DV FERYYKQHLARRLLTNKSVSDDSEKNMISKLKTECGCQFTSKLEG  
FRDMSISNTMDEFRQHLQATGVSLGGVDLTVRLTTGYWPTQSATPKCNIPPAPRHA  
FEIFRRFYLAHKSGRQLTLQHHMGSADLNATFYGPVKKEDGSEVGVGGAQVTGSNTRK  
HILQVSTFQM TILMFNNREKYTFEEIQQETDIPERELVRALQSLACGKPTQRVLTKEPK  
SKEIENGHIFTVNDQFTSKLHRVKIQTVAAKQGESDPERKETRQKVDDDRKHEIEAAIVRI  
MKS RKKM QHN VLVA E VTQQLKARFLPSPVVIKKRIE REY LART PEDR KVY TYVA

SEQ ID No: 48

MLRRVTVAACATRRKLCEAGRELAALWGIETRGRCEDSAAARPFPILAMPGRNKAKS  
TCSCPDLQPNGQDLGENSRVARLGADESEE E GRRG SLSNAGDPEIVKSPSDPKQYRYI  
KLQNGLQALLISDLSNMEGKTGNTTD EEEEEE VEEE EDDDED SGAEI EDD DEEGFDDE  
DEF DDE H D D D L D TED NE E E LE ERA E ARK KT TE KQS A AL CVGVGSFADPDDLPGLAH  
FLEHMVF MGS LKYPDENG FDAFLKKHGGSDNASTDCERTVFQFDVQRKYFKEALDRW

AQFFIHPLMIRDAIDREVEAVDSEYQLARPSDANRKEMLFGLSLARPGHMGKFFWGNA  
 ETLKHEPRKNNIDTHARLREFWMRYYSSHYMTLVQSKETLDTLEKWVTEIFSQIPNNG  
 LPRPNFGHLTDPFDTPAFNKLYRVVPIRKIHALTITWALPPQQHQHYRVKPLHYISWLVGH  
 EGKGSILSFLRKKCWALALFGGNGETGFEQNSTYSVFSISITLTDEGYEHFYEVAYTVFQ  
 YLKMLQKLGPEKRIFEIRKIEDNEFHYZEQTDPVEYVENMCENMQLYPLQDILTGDQLL  
 FEYKPEVIGEALNQLVPQKANLVLLSGANEKGCDLKEKWFGTQYSIEDIENSWGELWNS  
 NFELNPDLHLPAENKYIATDFTLKAFCDCPETEYPVKIVNTPQGCLWYKKDNKFKIPKAYIR  
 FHLISPLIQKSAANVVLDFVNILTHNLAEPAYEADVAQLEYKLVAGEHGLIIRVKGFNHK  
 LPLLFBQLIIDYLAEFNSTPAVFTMITEQLKKTYFNILKPETLAKDVRLLILEYARWSMIDKY  
 QALMDGLSLESLLSFVKEFKSQLFVEGLVQGNVTSTESMDFLKYVVVDKLNFKPLEQEMP  
 VQFQVVELPSGHHLCKVKALNKGDANSEVTVYYQSGTRSLREYTLMELLVMHMEEPCF  
 DFLRTKQTLGYHVYPTCRNTSGILGFSVTVGTQATKYNSEVVDKKIEEFLSSFEEKIENL  
 TEEAFNTQVTALIKLKECEDTHLGEEDVRNWNEVVTQQYLFDRILAHEIEALKSFSKSDLV  
 NWFKAHRGPGSKMLSVHAVGYGKYELEEDGTPSSEDSNSSCEVMQLTYLPTSPILLAS  
 VSSPLLISGLSQQHSTFSPTIK

SEQ ID No: 49

MGKQNSKLAPEVMEDLVKSTEFNEHELKQWYKGFLKDCPSGRLNLEEFQQLYVKFFPY  
 GDASKFAQHAFRTFDKNGDGTIDFREFICALSITSRGSFHQKLNWAFNMYDLDGDGKIT  
 RVEMLEIIIAIYKMVGTVIMMKMNEDGLTPEQRVDKIFSMDKNDDQITLDEFKEAAKS  
 DPSIVLLLQCDIQK

SEQ ID No: 50

MLGGSGSHGRRSLAALSQIAYQRNDDDEEEAARERRRARQERLRQKQEEESLGQVT  
 DQVEVNAQNSVPDEEAKTTNTQVEGDDEAAFLERLARREERRQKRLQEALERQKEF  
 DPTITDASLSPSRRMQNDTAENETTEKEEKSESQRQERYIEETETVTKSYQKNDWRDA  
 EENKKEDKEKEEEEEEEPKRGSIGENQIKDEKIKKDKEPKEEVKSFMDRKKGFTEVKSQ  
 NGEFMTHKLKHTENTFSRPGGRASVDTKEAEGAPQVEAGKRLEELRRRRGETESEEF  
 EKLKQKQQEAALELEELKKREERRKVLEEEEQRRKQEEADRKLREEEKRRRLKEEIER  
 RRAEAAEKRQKMPEDGLSDDKKPFKCFTPKGSSLKIEERAFLNKSQVKSSGVKSTHQ  
 AAIISKIDSRLAQYTSIAEGTKSAKPTKPAASDLPVPAEGVRNIKSMWEKGNVFSSPTAA  
 GTPNKETAGLKVGVSSRINEWLTKTPDGNKSPAPKPSDLRPGDVSSKRNLWEKQSVD  
 KVTSPTKV

SEQ ID No: 51

MSEHVEPAAPGPGPNNGGGPAPARGPRTPNLNPNPLINVRDRLFHALFFKMAVTYS  
 RLFPPAFRRLFEFFVLLKALFVLFLAYIHIVFSRSPINCLEHVRDKWPREGILRVEVRHN  
 SSRAPVFLQFCDSGGRGSFPGLAVEPGSNLDMEDEEEEELTMEMFGNNSIKFELDIEP  
 KVFKPPSSTEALNDSQEFPFPETPTKVWPQDEYIVEYSLEYGFLRLSQATRQRLSIPVM  
 VVTLDPTRDQCFGDRFSRLLLDEF LGYDDILMSSVKGLAENEENKGFLRNVSGEHYRF  
 VSMWMARTSYLAFAIMVI TLSVSMLLRYSHHQIFVFIVDLLQMLEMNMAIAFPAAPLLT  
 VIALVGMEA IMSEFFNDTTAFYIILIVWLADQYDAICC HTSTS KRHWLRFYLYHFAYA  
 YHYRFNGQYSSLALVTSWLFIQHSMIYFFHHYELPA ILQQVRIQEMLLQAPPLGP GTPTA  
 LPDDMNNNSGAPATAPDSAGQPPALGPV FELVSKERGWGSAEGSGGVLVGLQ

SEQ ID No: 52

MDTSRLGVLLSLPVLLQLATGGSSPRSGVLLRGCPTHCHCEPDGRMLLRVDCSDLGLS  
 ELPSNLSVFTSYLDLSMNNISQLLPNPLPSLRFLEELRLAGNALTYIPKGAF TGLYSLKVL  
 MLQNNQLRHVPTEALQNLRSLSLQSLR LDANHISYVPPSCFSGLHSLRHLWLD DNALTEIP  
 VQAFRSL SALQAMTLALNKIH HIPDYAFGNLSSLVVLHLHNNRIHSLGKKCFDGLHSLET  
 LDLN YNNLDEFPTAIRTLSNLKE LGFHSNNIRSIPEKA FVG NPSLITI HFYDNPIQFVG RSA  
 FQHLPELRTLTLNGASQITEFPDLTGTANLES LTGAQISSLPQTVCNQLPNLQVLD SY  
 NLLEDLPSFSVCQKLQKIDLRHNEIYEIKVDTFQQLLRLS LNLAWN KIAIIHPNAFSTLPS  
 LIKLDLSSNLLSSFPITGLHGLTHLKTGNHALQSLISSEN FPELKVIEMPYAYQCCAFGV  
 CENAYKISNQWNKGDNSSMDDLHKKDAGMFQAQDERDLED FLLDFEEDLKALHSVQC  
 SPSPGPKPC EHLLDGWLIRIGVWTIAV LA LTCNA VTSTVFRSPLYISPIKLLIGVIAAVN  
 MLTG VSSAVLAGVDAFTFGSFARHGAWWENGVGCHIGFLSIFASESSVFLTLAALER  
 GFSVKYSAKFETKAPFSSLKVIILLCALLALTMAAVPLLGGSKY GASPLCLPLFGE PSTM  
 GYMVALILLNSLCFLMMTIAYTKLYCNLDKG DLENIWDCSMVKHIA LLFTNCILNCPVAF  
 LSFSSLINLT FISPEVIK FILLVVVPLPACLNPLLYILFNPHFKEDLVSLRK QTYV WTRSKHP  
 SLMSINSDDVEKQSCDSTQALVTFTSSSITYDLPPSSVPSPAYPVTESCHLSSVA FVPC L

SEQ ID No: 53

KEQSELDQDLDDVEEVEEEETGEETKLKARQLTVQMMQNPQILAALQERLDGLVETPT  
 GYIESLPRVVKRRVNALKNLQVKCAQIEAKFYEEVHDLERKYAVLYQPLFDKRFEINAIY  
 EPTEEECEWKPDEEDEISEELKEKAKIEDEKKDEEKEDPKGIPEFWLTVFKNV DLLSDM  
 VQEHD EPILKHLKDIKVFKFSDAGQPMSVLEFH FEPNEYFTNEVLT KTYRMRSEPDDSD  
 PFSFDGPEIMGCTGCQIDWKKGKNVTLKTIKKQKHGRGTVRTVTKTVSND SFFNFFA

PPEVIPKFSAFDDDAEAILAADFEIGHFLRERIIPRSVLYFTGEAIEDDDDYDEEGEEAD  
EGYQLFEEVKSCSKLFQRWLQ

SEQ ID No: 54

MAQALPWLLLWMGAGVLPAHGTQHGIRLPLRSGLGGAPLGLRLPRETDEEPEEPGRR  
GSFVEMVDNLRGKSGQQGYVEMTVGSPPQTLNILVDTGSSNFAVGAAPHFLHRYYQ  
RQLSSTYRDLRKGVYVPYTQGKWEGETDLCAGFPLNQSEVLAvggsmiiggid  
HSLYTGSLWYTPIRREWYYEVIVRVEINGQDLKMDCKEYNyDKSIVDSGTTNLRLPKV  
FEAAVKSIAASSTEKFpdGFwlgeqlvcwqagtppwnifpvisllymgevtqnqsfriti  
LPQQYLRPVEDVATSQDDCYKFAISQSSTGTVMGAVIMEGFYVVFDRAKRIGFAVSAC  
HVHDEFRTAAVEGPFTLDMEDCGYNIPQTDESTLMTIAYVMAAICALFMLPLCLMVCQ  
WRCLRCLRQQHDDFADDISLLK

SEQ ID No: 55

MAATGTAAAAATGRLLLLLVGLTAPALALAGYIEALAANAGTGFAVAEPQIAMFCGKLN  
MHVNIQTGKWEPDPTGKSCFETKEEVLQYCQEMYPELQITNVMEANQRVSIDNWCR  
RDKKQCKSRVTPFKCLVGEFVSDVLLVPEKCQFFHKERMEVCENHQHWHTVVKEAC  
LTQGMTLYSYGMLLPCGVDQFHGTEYVCCPQTKIIGSVSKEEEEDEEEEEEDEED  
YDVYKSEFPTEADLEDFTEAAVDEDDEDEEEGEEVVEDRDYYYDTFKGDDYNEENPTE  
PGSDGTMDSKKEITHDVKAVCQEAMTGPCRAVMRWFDL SKGKCVRFIYGGCGGNR  
NNFESEDYCMAVCKAMIPPTPLPTNDVDVYFETSADDNEHARFQKAKEQLEIRHRNRM  
DRVKEWEEAELQAKNLPKAERQTLIQHFQAMVKALEKEAASEKQQLVETHLARVEAM  
LNDRRRMALENYLAALQSDPPRPHRILQALRRYVRAENKDRHTIRHYQHVLAVDPEKA  
AQMKSQVMTHLHIEERRNQSLSLYKVPYVAQEIQEEIDELLQEQRADMDQFTASISE  
TPVDVRVSSEESEEIPPFHPFHPFPALPENEDTQPELYHPMKKGSGVGEQDGGGLIGAE  
EKVINSKNKVDENMVIDETLDVKEMIFNAERVGLEEERESVGPLREDFSLSSALIGLL  
VIAVAIATVIVISLVMRLKRQYGTISHGIVEVDPMLTPEERHLNKMQNHYENPTYKYLEQ  
MQI

SEQ ID No: 56

MRSPATGVPLPTPPPLLLLLLPPPLLGDQVGPCRSLGSRGRGSSGACAPMGWLC  
PSSASNLWLYTSRCRDAGTELTHGLVPHDGLRVWCPSEAHIPPAPEGCPWSCR  
LLGIGGHLSHQKLTPEEHPCLKAPRRLRCQSCKLAQAPGLRAGERSPEESLGGRRKR  
NVNTAPQFQPPSYQATVPENQPAGTPVASLRAIDPDEGEAGRLEYTMDALFDSRSNQF

FSLDPTVTGAVTTAEELDRETKSTHVFRVTAQDHGMPRRSALATLTLVTDTNDHDPVFE  
QQEYKESLRENLEVGYEVLTVRATDGDAPPNANILYRLLEGSGGPSEVFEIDPRSGVI  
RTRGPVDREEVESYQLTVEASDQGRDPGP.RSTTAAVFLSVEDNDNAPQFSEKRYVV.  
QVREDVTPGAPVLRVTASDRDKGSNAVHYSIMSGNARGQFYLDAQTGALDVVSPLDY  
ETTKEYTLRVRAQDGGRPPLSNVGLTVQVLDINDNAPIFVSTPFQATVLESVPLGYLV  
LHVQAIDADAGDNARLEYRLAGVGHDFFPTINNGTWISVAAELDREEVDFYSGVEAR  
DHGTPALTASASVSVTLDVNDNNPTFTQPEYTVRLNEDAAGTSVVTSAVDRDAHS  
VITYQITSGNTRNRFITSQSGGGLVSLALPLDYKLERQYVLAVTASDGTRQDTAQIVVN  
VTDANTHRPVFQSSHYTNVNEDRPAGTTVVLISATDEDTGENARITYFMEDSIPQFRID  
ADTGAVTTQAELDYEDQVSYTLAITARDNGIPQKSDDTYLEILVNDVNDNAPQFLRDSYQ  
GSVYEDVPPFTSVLQISATDRDGLNGRWFYTFQGGDDGDGDFIVESTSGIVRTLRRLD  
RENVQAQYVLRAYAVDKGMPPARTPMEVTVLVDVNDNPPVFEQDEFDVFVEENSPIGL  
AVARVTATDPDEGTNAQIMYQIVEGNIPEVFQLDIFSGELTALVLDYEDRPEYVLVIQAT  
SAPLVS RATVHVRLLDRNDNPPV LGNFEILFNNYVTNRSSFP GGAIGRVPAHD PDISD  
SLTYSFERGNELSLVLLNASTGELKLSRALDNNRPLEAIMSVLSDGVHSVTAQC ALRVT  
IITDEM LTHSITLRLEDMSPERFLSP LLGLFIQAVAATLATPPDHVVVFNVQRDT DAPGGH  
ILNVSLSVGQPPGP GGGPPFLPS EDLQERLYLNRSLLTAISAQRVLPFDDN ICLREPCEN  
YMRCVSVLRFDSSAPFIASSVLF RPIHPV GGLRCRCPPGFTGDYCETEVDLCY SRPCG  
PHGRCRSREGGYTCLCRDGYTGEHCEVSARS GRCTPGVCKNGGTCVNLLVGGFKCD  
CPSGDFEKPYCQV TTRSFPAHS FITFRGLRQRFHFTLALSFA TKERDGLL YN GRFNEK  
HDFVALEVIQE QVQLTFSAGE STTVSPFVP GG VSDGQWHTVQLKYYNKPLL GQTGLP  
QGPSEQKVAVVTVDG CDTGVALRFGS VLGN YSCAAQGTQGGSKKSLDTGP LLGGV  
PDL PESFPVRMRQFVGCMRNLQVDSR HIDMADFI ANNGTVP GCPAKKNV CDSNTCHN  
GGTCVNQWDAFSC ECPLGF GGKSCA QEMANPQHFLGSSLVAWHGLSLP ISQPWYLSL  
MFRTRQADGVLLQAITRGRSTITLQLREGHV MLSVE GTGLQASSLRLEPGR ANDGDWH  
HAQLALGASGGPGHAILSF DYGQQRAEGNLGPR LHGLHLSN ITVGGIPGPAGGVARGF  
RGCLQGV RVSDTPEGVNSLDPSHGESINVEQGCSLPDCDSNP CPANSYCSNDWDSY  
SCSCDPGYYGD NCTNVCDLN PCEHQ SVCTR KPSAP HG YTCEC PPNYLGP YCETRIDQ  
PCPRGWWGHPTCG PCNC DVSKGF DPD CNKTSG ECHCK ENHYRPPG SPTCLL CDCYP  
TGSLSRVCD PEDGQCPCK PGVIGRQCD RC DN PFAEV TTNG CEV NYDSCP RAI EAGI W  
WPRTRFGLP AAAPCPKG SF GTAVRHC DEHR GWLPPN LF NCTSIT FSEL KGFAE RLQRN  
ESGLDSGRSQQQL ALLLRN ATQHTAGYFGSDV KVAYQL ATRLLA HESTQRGFG LSAT QD  
VHF TENLL RVGS ALL DTANKRHW ELIQ QT EGGTA WLLQH YEAYA SALA QNMR HTY LSP  
FTIVTPNIVISV VR LDKG NFAGA KLPR YEA LRGEQ PPD LETT VILP ES VF RET PPV VR PAG

PGEAQEPEELARRQRRHPELSQGEAVASVIYRTLALLPHNYDPDKRSLRVPKRPIINT  
 PVVSISVHDDEELLPRALDKPVTQFRLLETEERTKPICVFVNHSILVSGTGGWSARGC  
 EVVFRNESHVSCQCNCNHMTSFAVLMDVSRRNGEILPLKTLTYVALGVTIAALLTFFFLLT  
 LLRILRSNQHGIRRNLTAAAGLAQLVFLLGINQADLPFACTVIAILLHFLYLCTFSWALLEAL  
 HLYRALTEVRDVNTGPMRFYYMLGWGVPAFITGLAVGLDPEGYGNPDFCWLSIYDTLI  
 WSFAGPVAFAVSMSVFLYILAARASCAAQRQGFKEKKGPVSGLQPSFAVLLLSATWLLA  
 LLSVNSDTLLFHYLFACTNCIQGPFIFLSYVVLSEVRKALKACSRKPSPDPALTAKSTL  
 TSSYNCSPSPYADGRLYQPYGDSAGSLHSTSRSGKSQPSYIPFLLREESALNPQGQGPPG  
 LGDPGSLFLEGQQHQHDPDTSDSDLSLEDDQGSYASTHSSDSEEEEEEEA  
 PGEQGWDSLLGPAGERLPLHSTPKDGGPGPGKAPWPGDFGTTAKESSGNGAPEERL  
 RENGDALSGREGSLGPLPGSSAQPHKGILKKCLPTISEKSSLRLPLEQCTGSSRGSSA  
 SEGSRGGPPPRPPPRQSLQEQLNGVMPIAMSIKAGTVDEDSSGSEFLFFNFLH

SEQ ID No: 57

MGKGGNQGEGAAEREVSVPTFSWEIJKHNLRTDRWLVIDRKVYNITKWSIQHPGGQ  
 RVIGHYAGEDATDAFRAFPDLEFGKFLKPLLIGELAPEEPSQDHGKNSKITEDFRALR  
 KTAEDMNLFKTNHVFFLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWL  
 QHDYGHLSVYRKPKWNHLVHKFVIGHLK GASANWWNHRHFQHHAKPNIFHKDPDVNM  
 LHVFVLGEWQPIEYGKKKLKYLPYNHQHEYFFLIGPPLIPMYFQYQIIMTMIVHKNWVDL  
 AWAWSYYIRFFITYIPFYGILGALLFLNFIRFLESHWFVVVTQMNHIVMEIDQEAYRDWFS  
 SQLTATCNVEQSFFNDWFSGHNFQIEHHLFPTMPRHLHKIAPLVKSLSAKHGIYEQE  
 KPLLRAALDIIRSLKKSGKLWLDAYLHK

SEQ ID No: 58

MEDLDQSPLVSSSDSPPRPQPAFKYQFVREPEDEEEEEEEEEEDEDLEELEVLER  
 EFSELEYSEMGSFSVSPKAESA VIVANPREIIVKNKDEEEKLVSNNILHNQQUELPTALT  
 KLVKEDEVVSSEKAKDSFNEKRVAVEAPMREEYADFKP FERVWEVKDSKEDSDMLAA  
 GGKIESNLESKVDKKCFADSLEQTNHEKDSESSNDDTSFPSTPEGIKDRSGAYITCAPF  
 NPAATESIATNIFPLLGDPTSENKTDEKKIEEKKAQIVTEKNTSTKTSNPFLVAAQDSETD  
 YVTTDNLTKVTEEVANMPEGLTPDLVQEACESELNEVTGT KIA YETKMDLVQTSEVMQ  
 ESLYPAAQLCPSFEESEATPSPVLPDIVMEAPLNSAVPSAGASVIQPSSS PLEASSVNYE  
 SIKHEPENPPPYEEAMS VSLKKVSGIKEEIKE PENINAALQETEAPYISIACDLIKETKLSA  
 EPAPDFSDYSEMAKVEQPVPDHSELVEDSSPDSEPVDLFSDDSIPDVPQKQDETVMLV  
 KESLTETSFESMIEYENKEKLSALPPEGGKPYLESFKLSLDNTKDTLLPDEVSTLSKKEKI

PLQMEELSTAVYSNDDLFISKEAQIRETETFSDSSPIEIIDFPTLISSKTDASFSLAREYT  
 DLEVSHKSEIANAPDGAGSLPCTELPHDLSLKNIQPKVEEKISFSDDFSKNGSATSKVLL  
 LPPDVSALATQAEIESIVKPKVLVKEAEKKLPSDTEKEDRSPSAIFSAELSKTSVV DLLY  
 RDIKKTGVVFGASLFLLSLTVFSIVSVTAYIALALLSVTISFRIYKGVIQAIQKSDEGH PFR  
 AYLESEVAISEELVQKYSNSALGHVNCTIKELRRFLVDDLVDLSKFAVLMWVFTYVGAL  
 FNGLTLLILALISLFSVPVIYERHQAQIDHYLGLANKNVKDAMAKIQAKIPGLKRKAE

SEQ ID No: 59

MAAETLLSSLLGLLLLGLLL PASLTGGVGSLNLEELSEMRYGIEILPLPVMMGQS QSSDV  
 VIVSSKYKQRYE CRLPAGAIHFQRERE EETPAYQGPGIPELLSPMRDAPCLLKT KDWWT  
 YEFCYGRHIQQYHMEDSEIKGEVLYLGYYQSAFDWDDETAKASKQHRLKRYHSQTYG  
 NGSKCDLN GRPREAEVRFLCDEGAGISGDYIDRVDEPLSCSYVLTIRTPRLCPHPLL RP  
 PPSAAPQAILCHPSLQPEEY MAYVQRQAVDSKQYGDKII EELQDLGPQVWSETKSGVA  
 PQKMAGASPTKDDSKD SDFWKMLNEPEDQAPGEEVPAEEQDPSPEAADSASGAPN  
 DFQNNVQVKVIRSPADLIRFIEELKG GTKKGKP NIQEQPVDDAAEV PQREPEKER G DP  
 ERQREMEEEDED EDEDEDERQ LLGEFEKELEGILLPSDRDRLRSEVKA GMERE LE  
 NIIQEASP ALPP TEKELDPD GLKKE SERDR AMLALTSTLNKL IKRLEEKQSPELVKKH KKK  
 RVVPKKPPPSPQPT EEDPEHRV RVRVTKLRLGGPNQDLTVLEMKREN PQLKQIEGLVK  
 ELLEREGLTAAGKIEIKIVRPWAEGTEEGARWL TDEDTRNLKEIFFNILVPGAE EAQKER  
 QRQKELESNYRRVWGSPGEGTGDLDEFDF

SEQ ID No: 60

MRLPGAMPALALKGELL LLSLLLLEPQISQGLVVT PPGPELVL NVSSTFVLTCSGSAPV  
 VWERMSQEPPQEMAKAQDGT FSSVLTNTL GTGEYFCTHND SRGLET DERKRL YI  
 FVPDPTVGFLPNAEELFIFL TEITEITIPCRV TDPQLV VT LHEKKGDVALPV PYDHQRGF  
 SGIFEDRSYICKTTIGDREV DSDAYYVYRLQVSSINVS NAVQT VVRQGENITLM CIVIGN  
 EVVNFEWTYPRKEVIGRLVEPV TDFL LDMPYHIRSILHIPS A ELED SGTYTCNV TESVND  
 HQDEKAINITV VESGYVRLLGEVGT LQFAELHRSRTLQVVF EAYPPPTV LWFKDNRTLG  
 DSSAGEIALSTRNVSETRYVSELTL VRVKA EAGHYTMRAFHEDA E VQLSFQLQIN VPV  
 RVLELS ESHPD SGEQTVRCRGMPQPN IWSACRDLKRC PRELPPTLLGNSSEE ESQ  
 LETNV TYWEEEQEFEVV STLR LQHV DRPLS VR CTLRNAVGQDTQEIVVPHSLPFKV  
 VV ISAILALV VLT IISL IMLWQKKPRYEIRWKVIESVSSDGHEYIYVDPMQLPYDSTWELPR  
 DQLV LGRT LGSGAFGQV VEATAHGLSHSQATMKVAVKMLKSTAR SSEKQALMSELKIM  
 SHLGPHLN VVNLLGACTKGGPIYIITEYCRYGDLV DYLHRNKHTFLQHHSDKRRPPSAEL

YSNALPVGLPLPSHVSLTGESDGGYMDMSKDESVDYVPMNDMKGDVKYADIESSNYM  
 APYDNYVPSAPERTCRATLINESPVLSYMDLVGFSYQVANGMEFLASKNCVHRDLAAR  
 NVLICEGKLVKICDFGLARDIMRDSNYISKGSTFLPLKWMAPESIFNSLYTTLSDVWSFGI  
 LLWEIFTLGGTPYPELPMNEQFYNAIKRGYRMAQPAHASDEIYEIMQKCWEEKFEIRPP  
 FSQLVLLLERLLGEGYKKYQQVDEEFLRSDHPAILRSQARLPGFHGLRSPLDTSSVLY  
 TAVQPNEGNDYIIPLPDPKPEVADEGPLEGSPSLASSTLNEVNTSSTISCDSPLEPQDE  
 PEPEPQLELQVEPEPELEQLPDSGCPAPRAEAEDSFL

SEQ ID No: 61

MGAARGSPARPRRLPLLSVLLLPLLGGTQTAIVFIKQPSSQDALQGRALLRCEVEAPG  
 PVHVVWLLDGAPVQDTERRFAQGSSLSFAAVDRLQDSGTFCVARDVTGEEARSAN  
 ASFNWKIEAGPVVLKHPASEAEIQPQTQVTLRCHIDGHPRPTYQWF RDGTPLSDGQSN  
 HTVSSKERNLTLPAGPEHSGLYSCCAHSAGQACSSQNFTLSIADES FARVVLAPQD  
 VVVAR YEEAMFHCQFSAQPPPSLQWLFEDETPTINRSRPPHLRRATVFANGSLLTQV  
 RPRNAGIYRCIGQQQRGPPIILEATLH LAEIEDMPLFEPRVFTAGSEERVTC LPPKGLPE  
 PSVWWEHAGVRLPTHGRVYQKGHELVLANIAESDAGVYTCHAANLAGQRRQDVNITV  
 ATVPSWLKKPQDSQLEEGKPGYLDCLTQATPKPTVVWYRNQMLISEDSRFEVFKNGL  
 RINSVEVYDGTWYRCMSSTPAGSIEAQARVQVLEKLKFTPPPQPQQCMEFDKEATVPC  
 SATGREKPTIKWERADGSSLPEWVTDNAGTLHFARVTRDDAGNYTCIASNGPQGQIRA  
 HVQLTVAVFITFKVEPERTTVYQGHTALLQCEAQGDPKPLIQWKKGDRILDPTKLGPRM  
 HIFQNGSLVIHDVAPEDSGRYTCIAGNSCNIKHTEAPLYVVDKPVPEESEGPGSPPP  
 YK MIQTIGLSVGA AVAYIIAVGLMFYCKKRCKAKRLQKQPEGEPEMECLNGGPLQNGQP  
 SAEIQEEVALTSLGSGPAATNKRHSTS D KMHF PRSSLQPI TLGKSEFGEVFLAKAQGL  
 EEGVAETLVLVKS LQSKDEQQQLDFRRELEMFGKLNHANVVRLLGLCREAEPHYMVLE  
 YVDLGDLKQFLRISKSKDEKLKSQPLSTKQKV ALCTQVALGMEHLSNNRFVHKDLAARN  
 CLVSAQRQVKVSALGLSKDVYNSEYYHFRQAWVPLRWMSPEAILEGDFSTKSDVWAF  
 GVLMWEVFTHGEMPHGGQADDEVLA DLQAGKARLPQPEGCPSKLYRLMQRCWALSP  
 KDRPSFSEIASALGDSTVDSKP

SEQ ID No: 62

MGCKGDASGACAAGALPVTGVCYKMGVLVVLTVLWLFSSVKADSKAITTS LTT KWFST  
 PLLLEASEFLAEDSQEKFWNFVEASQNI GSSDH DGT DYS YY HAILEAAFQFLSPLQQNL  
 FKFCLSRSYSATIQAFQQIAADEPPPEGCNSFFSVHGKKT CESDT LEALLTASERPKP  
 LLFKGDHRYPSSNPESPV VIFYSEIGSEEFSNFHRQLISKSAGKINYVFRHYIFNPRKEP

VYLSGYGVLAIKSTEYAKDDTQVKGTEVNTTVIGENDPIDEVQGFLFGKLRDLHPDLE  
 GQLKELRKHLVESTNEMAPLKVVWQLQDLSFQTAARILASPVELAVVMKDLSQNFPTKA  
 RAITKTAVSSELRTVEEENQKYFKGTLGLQPGDSALFINGLHMDLDTQDIFSLFDVLRNE  
 ARVMEGLHRLGIEGLSLHNVLKLNIPSEADYAVDIRSPAISWVNNEVDSRYNSWPSS  
 LQELLRPTFPGVIRQIRKNLHNMFIVDPAHETTAELMNTAEMFLSNHIPLRIGFIVVND  
 SEDVDGMQDAGVAVLRAYNYVAQEVDYHAFQTLTHIYNKVRTGEKVKEHVSVLEK  
 KYPYVEVNSILGIDSAYDRNRKEARGYYEQTGVGPLVLFNGMPFEREQLDPDELETI  
 TMHKILETTFFQRAVYLGELPHDQDVVEYIMNQPNVPRINSRILTAERDYLDLTASNN  
 FFVDDYARFTILDSQGKTAAVANSMNYLTKGMSKIEYDDSFIRPVTFWIVGDFDSPS  
 GRQLLYDAIKHQKSSNNVRISMNINPAAKISYENTQISRAIWAALQTTSNAAKNFIKMA  
 KEGAAEALAAGADIAEFSGGMDLSLFKEVFESSKMDFILSHAVYCRDVLKLKGQRAV  
 ISNGRIIGPLEDSELFNQDDFHLLENIILKTSGQKIKSHIQQLRVEEDVASDLVMKVDALLS  
 AQPKGDPRIEYQFFEDRHSAIKLRPKEGETYFDVVAVVDPVTREAQRLAPLLLVLQA  
 MNLRVFMNCQSKLSDMPLKSFYRYVLEPEISFTSDNSFAKGPIAKFLDMPQSPLFTLNL  
 NTPESWMVESVRTPYDLDNIYLEEVDSVVAEYELEYLLLEGHCYDITTGQPPRGLQFT  
 LGTSANPVIVDTIVMANLGYFQLKANPGAWILRLRKGRSEDIYRIYSHDGTDSPPDAEV  
 VIVLNNFKSKIIVKVQKKADMVNEDLLSDGTSENESGFWDSFKWGFTGQKTEEVKQD  
 KDDIINIFSVASGHLYERFLRIMMLSVLKNTKTPVKFWFLKNYLSPTFKEFIPYMANEYNF  
 QYELVQYKWPRWLHQQTKEQRIIWGYKILFLDVLFPLVVDKFLFVDADQIVRTDLKELRD  
 FNLDGAPYGYTPFCDSRREMDGYRFWKGWASHLAGRKYHISALYVVDLKKFRKIAA  
 GDRLRGQQYQGLSQDPNSLSNLDQDLPNNMIHQVPIKSLPQEWLWCETWCDDASKKRA  
 KTIDLCNNPMTKEPKLEAAVRIVPEWQDYDQEIKQLQIRFQKEKETGALYKEKTKEPSRE  
 GPQKREEL

SEQ ID No: 63

MGALARALLPLLAQWLLRAAPELAPAPFTLPLRVAAATNRVVAPTPGPGTPAERHADG  
 LALALEPALASPAGAANFLAMVDNLQGDSGRGYYLEMLIGTPPQKLQILVDTGSSNFAV  
 AGTPHSYIDTYFDTERSTSSTYRSKGFDVTVKYTQGSWTGFVGEDLVTIPKGNTSFLVNIA  
 TIFESENFFLPGIKWNGILGLAYATLAKPSSLETFFDSLVTQANIPNVFSMQMCGAGLP  
 VAGSGTNGGSLVGGIEPSLYKGDIWYTPIKEEWYYQIEILKLEIGGQSLNLDREYNAD  
 KAIVDSGTTLLRPQKVFDAVVEAVARASLIPEFSDGFWTGSQLACWTNSETPWSYFPK  
 ISIYLRDENSSRSFRITILPQLYIQPMMGAGLNYPEYCFGISPSTNALVIGATVMEGFYVIF  
 DRAQKRVGFAASPCAEIAGAAVSEISGPFSTEDVASNCVPAQSLSEPILWIVSYALMSVC  
 GAILLVIVLLLLPFRCQRPRDPEVVNDESSLVRHRWK

SEQ ID No: 64

MDVKERRPYCSLTCSRREKERRYTNSSADNEECRVPTQKSYSSETLKAFDHDSRLL  
 YGNRVKDLVHREADEFTRGQNFTLRQLGVCEPATRRGLAFCAEMGLPHRGYSISAG  
 SDADTENEAVMSPEHAMRLWGRGVKSGRSSCLSSRSNSALTLDTEHENKSDSENEQ  
 PASNQQQSTLQPLPPSHKQHSAQHHPSITSNRRNQSPAPPALPAELQTTP  
 ESVQLQDSWVLGSNVPLESRHFLFKTGTGTTPLFSTATPGYMASGSVYSPPTRPLPR  
 NTLSRAFKFKSSKYCSWKCTALCAVGVSVLLAILLSYFIAMHLFGLNWQLQQTENDT  
 FENGKVNSDTMPTNTVSLPSGDNGKLGGFTQENNTIDSGELEDIGRRAIQEIPPGIFWRS  
 QLFIDQPQFLKFNISLQKDALIGVYGRKKLPPSHTQ

SEQ ID No: 65

MATQADLMELDMAMEPDRKA AVSHWQQQS YLDSGIHSGATTAPSLSGKGNPEEE DV  
 DTSQVLYEW EQGFSQSFTQE QVADIDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQF  
 DAAHPTNVQRLAEP SQLKH AVVN LINYQDDAELATRAIPELT KLLNDEDQVV NKA AV  
 MVHQLSKKEASRHAIMRSPQM VS AIVRTMQNTNDVETARCTAGTLHNLSHHREG LLA IF  
 KSGGIPALVKMLGSPVDSVLFYAITTLHNLLLHQEGAKMAVRLAGGLQKMVALLNKTNV  
 KFLAITTDCLQILAYGNQESKLIILASGGPQALVNIMRTYTYEKL WTTSRVLKVLSVCSS  
 NKPAIVEAGGMQALGLHLDPSQRLVQNCLWTLRNLSDAATKQEGMEGLGTLVQLLG  
 SDDINVTCAGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRH  
 LTSRHQEAEAMAQN A VR LH YGLPVV V KLLHPPSHWPLIKATVGLIRNLAC PAN HAPL RE  
 QGAIPRLVQLLVRAHQDTQRRRTSMGGTQQQFVEGVRMEEIVEGCTGALHILARDVHNR  
 IVIRGLNTIPLFVQLLYSPIENIQRVAAGVLCELAQDK EAAEAIAEAGATA PLTELLHSRNE  
 GVATYAAAVLFRMSEDKPQDYKKRLSVELTSSLFRTEPMAWN ETADLGLD IGAQGEPL  
 GYRQDDPSYRSFHSGGYGQDALGMDPMMEHEMGHHPGADYPVDGLPD LGHAQDL  
 MDGLPPGDSNQLAWFD TDL

SEQ ID No: 66

MAAASYDQLLKQVEALKMENSNL RQELEDNSNHLTKLETEASNMKEVLKQLQGSIEDE  
 AMASSGQIDLLERLKELNLDSSNF PGVKLRSKMSLRSYGSREGSVSSRSGE CSPV PMG  
 SFPRRGFVNGSRESTGYLEELEKERSLLLADLDKEEKEKD WYYAQLQNLTKRIDSLPLT  
 ENFSLQTDMTRRQLEYEARQIRVAMEEQLGTCQDM EKRAQRRIARIQQIEKDILRIRQLL  
 QSQATEAERSSQNKHETGSHDAERQNEGQGVGEINMATSGNGQGSTTRMDHETASV  
 LSSSSTHSAPRRLTSHLGTKIRAYCETCWEWQEAHEPGMDQDKNPMPAPVEHQICPA

VCVLMKLSFDEEHRHAMNELGGLQIAEELLQVDCEMYGLTNDHYSITLRRYAGMALTNL  
TFGDVANKATLCMSKGCMRALVAQLKSESEDLQQVIASVRNLSWRADVNSKKTLREV  
GSVKALMECALEVKKESTLKVSLWNLSAHCTENKADICAVDGALAFLVGTLTYRSQ  
TNTLAIIESGGGILRNVSSLIATNEDHRQILRENNCLQTLLQHLKSHSLTIVSNACGTLWNL  
SARNPKDQEALWDMGAVSMLKNLIIHSKHKMIAMGSAAALRNLMANRPAKYKDANIMSP  
GSSLPSLHVRKQKALEAELDAQHLSETFDNIDNLSPKASHRSKQRHKQSLYGDYVFDT  
NRHDDNRSDFNTGNMTVLSPYLNTTVLPSSSSRGSDLSSRSEKDRSLERERGIGLG  
NYHPATENPGTSSKRGLQISTTAAQIAKVMEEVSAIHTSQEDRSGSTTELHCVTDERN  
ALRRSSAAHTHSNTYNFTKSESNRTCSMPYAKLEYKRSSNDSLNSVSSSDGYGKRG  
QMCKPSIESYSEDDESKFCSYGQYPADLAHKIHSANHMDNDGELDTPINYSLKYSDEQL  
NSGRQSPSQNERWARPKHIIIDEIKQSEQRQSRNQSTTYPVYTESTDDKHLKFQPHFG  
QQECVSPYRSRGANGSETNRVGSNHGINQNVSQSLCQEDDYEDDKPTNYSERYSEEE  
QHEEEERPTNYSIKYNEEKRHVDQPIDYSLKYATDIPSSQKQSFSFSKSSSGQSSKTEH  
MSSSENTSTPSSNAKRQNQLHPSSAQSRSGQPQKAATCKVSSINQETIQTYCVEDTP  
CFSRCSSLSSLSSAEDEIGCNQTTQEADSANTLQIAEIKEKIGTRSAEDPVSEVPAVSQH  
PRTKSSRLQGSSLSESARHKAVEFSSGAKSPSKSGAQTPKSPPEHYVQETPLMFSRC  
TSVSSLDSFESRSIASSVQSEPCSGMVGIIISPSDLPDSPGQTMPPSRSKTPPPPQTA  
QTKREVPKNKAPTAEKRESGPQAAVNAAVQRVQVLPADTLLHFATESTPDGFSCSS  
SLSALSLDEPFIQKDVELRIMPPVQENDNGNETESEQPKESNENQEKEAETIDSEKDLL  
DDSDDDDIEILEECIISAMPTKSSRKAKKPAQTASKLPPPVARPKPSQLPVYKLLPSQNRL  
QPQKHVSFTPQDDMPRVYCVEGTPINFSTATSLSDLTIESPPNELAAGEGVRGGAQSG  
EFEKRDTIPTEGRSTDEAQGGKTSSVTIPELDDNKAEEGDLAECINSAMPKGKSHKPFR  
VKKIMDQVQQASASSSAPKNQLDGKKKPTSPVKPIPQNTEYRTRVRKNADSKNNLN  
AERVFSDNKDSKKQNLKNNSKDFNDKLPPNNEDRVRGSFAFDSPHHYTPIEGTPYCFSR  
NDSLSSLDFFDDDVDLREKAELRKAKENKESEAKVTSHTELTSNQQSANKTQAIAKQP  
INRGQPKPILQKQSTFPQSSKDIPDRGAATDEKLQNFAIENTPVCFSHNSSLSSLDIDQ  
ENNNKENEPIKETEPPDSQGEPSKPQASGYAPKSFHVEDTPVCFSRNSSLSSLSIDSED  
DLLQECISSAMPKKKPSRLKGDNKEHSPRNMGGILGEDLTLKDIQRPDSEHGLSPD  
SENFDWKAIQEGANSIVSSLHQAAAACLSRQASSDSDSILSLKSGISLGSPFHLPDQE  
EKPFITSNKGPRIKPGKSTLETKKIESESKGIGGGKKVYKSLITGKVRNSEISGQMKQ  
PLQANMPISRGRTMIHIPGVRNSSSTPVSKKGPPLKTPASKSPSEGQTATTSPRGA  
KPSVKSELSPVARQTSQLGGSSKAPSRSRSGSRDSTPSRPAQQPLSRPIQSPGRNSISPG  
RNGISPPNKLSQLPRTSSPSTASTKSSGSGKMSYTSPGRQMSQQNLTKQTGLSKNASS  
IPRSESASKGLNQMNNNGANKKVELSRMSSTKSSGESDRSERPVLVRQSTFIKEAP

SPTLRRKLEESASFESLSPSSRPASPTRSQAQTPVLSPLPDMSLSTHSSVQAGGWRK  
 LPPNLSPTIEYNDGRPAKRHDiarshsespsrlpinrsgtwkrehskhssslprvstwr  
 RTGSSSILSASSESEAKSEDEKHVNsisgtkqskenvsaqtwrkikenefsptn  
 STSQTVSSGATNGAESKTLIYQMAPAVSKTEDVVVRIEDCPINNPRSGRSPTGNTPPVI  
 DSVSEKANPNIKDSKDNQAKQNNGSVPMTVGLENRLNSFIQVDAPDQKGTEIKPG  
 QNNPVPVSETNESSIVERTPFSSSSSKHSSPSGTVAARVTPFNYNPSPRKSSADSTSA  
 RPSQIPTPVNNNTKKRDSKTDTESSGTQSPKRHSGSYLVTSV

SEQ ID No: 67

MTAVHAGNINFKWDPKSLEIRTLAVERLLEPLVTQVTLVNTNSKGPSNKKRGRSKKAH  
 VLAASVEQATENFLEKGDKIAKESQFLKEELVVAVEDVRKQGDLMKAAAGEFADDPCS  
 SVKRGNMVRAAPALLSAVTRLLILADMADVYKLLVQLKVVEDGILKLRNAGNEQD LGNQ  
 YKALKPEVDKLNIMA AKRQQELKDVGHRDQMAAARGILQSNVPILYTASQACLQHPDVA  
 AYKANRDLIYKQLQQAVTGISNAAQATASDDASQHQGGGGELAYALNNFDKQIIVDPL  
 SFSEERFRPSLEERLESIISGAALMADSSCTRDRRERIVAECNAVRCRTCVSEYMG  
 NAGRKERSDALNSAIDKMTKKTRDLRRQLRKAVMDHVSDSFLETNVPLLVLIEAKNGN  
 EKEVKEYAQVFREHANKLIEVANLACISNNEGVKLVRMSASQLEAGCPQVINAATWA  
 LAPKPQSKLAQENMDLFKEQWEKQVRVLTDADDDITSIDDFLAVSENHILEDVNKCIAL  
 QEKDVGDLRTAGAIRGRAARVIVHVTSEMDNYEPGVYTEKYLEATKLLNTVMPRFTE  
 QVEAAVEALSSDPAQPMDENEFIDASRLVYDGIRDIRKAVLMIRTPEELDDSDFETEDFD  
 VRSETS VQTEDDQLIAGQSARAIMAQLPQEQQAKIREQVASFQEEKSKLDAEVSKWDD  
 SGNDIIVLAKQMCMIMMEMTDFTRGKGPLKNTSDVISA AKKIAEAGSRMDKLGR TIRDH  
 CPDSACKQDLLAYLQRIALYCHQLNICSKVKAEVQNLGGELVSGNCDCGALQGLKG  
 WPPPLCLATHWVDSAMS LIQAAKNLMNAVQTVKASYVASTKYQKSQGMASLNLP AVS  
 MKMKAPEKKPLVKREKQDETQTKIKRASQKKHVNPVQALSEFKAMDSI

SEQ ID No: 68

MTSATSPIILKWDPKSLEIRTLTVERLLEPLVTQVTLVNTSNKGPSGKKRGRSKKAHVL  
 AASVEQATQN FLEKGGEQIAKESQDLKEELVAAVEDVRKQGETMRIASSEFADDPCSSVK  
 RGTMVRAARALLSAVTRLLILADMADVMRLLSHLKIVEEALEAVKNATNEQDLANRFKEF  
 GKGMVKLYVAARRQQELKDPHCRDEMAAARGALKKNATMLYTASQAFLRHPDVAAT  
 RANRDYVFKQVQEAIAGISNAAQATSP TDEAKGHTGIGELAAALNEFDNKIILDPMTFSE  
 ARFRPSLEERLESIISGAALMADSSCTRDRRERIVAECNAVRCQALQD LSEYMNNTGR  
 KEKGDP LNIAIDKMTKKTRDLRRQLRKAVMDHISDSFLETNVPLLVLIEAKSGNEKEVK

EYAQVFREHANKLVEVANLACSIQNNEEGVKLVRMAATQIDSLCPQVINAALTAAARPQS  
 KVAQDNMDVFKDQWEKQVRVLTEAVDDITSVDDFLSVSENHILEDVNKCIALQEGDVD  
 TLDRTAGAIRGRAARVIHINAEMENYEAGVYTEKVLEATKLLSETVMPRFAEQVEVAIEA  
 LSANVPQPFEENEFIDASRLVYDGVRDIRKAVLMIRTPEELEDDDFEQEDYDVRRGTS  
 VQTEDDQLIAGQSARAIMAQLPQEEKAKIAEQVEIFHQEKSKLDAEVAKWDDSGNDIIVL  
 AKQMCMIMMEMTDFTRGKGPLKNTSDVINAACKIAEAGSRMDKLARAVADQCPDSACK  
 QDLLAYLQRIALYCHQLNICKVKAEVQNLGGELIVSGTGVQSTFTFYEVDCDVIDGGR  
 ASQLSTHLPTCAEGAPIGSGSSDSSMLDSATSLIQAAKNLMNAVLTVKASYVASTKYQ  
 KVYGTAAVNSPVVSWKMKAPEKKPLVKREKPEEFQTRVRRGSQKKHISPVQALSEFKA  
 MDSF

SEQ ID No: 69

MDDSEVESTASILASVKEQEAQFEKLTRALEEERRHVSQAQLERVRVSPQDANPLMANG  
 TLTRRHQNQRFVGADLERQKFSDLKLNGPQDHSHLLYSTIPRMQEPMQIVETYTEED  
 PEGAMSVSVSVESTDGGTTRRTETTVKKVVKTVTTRTVQPVAMGPGLPVDASSVSNNY  
 IQLTGRDFRKNGNGPGPYVGQAGTATLPRNFHYPPDGYSRHYEDGYPGGSDNYGSL  
 SRVTRIEERYRPSMEGYRAPSRQDVYGPQPQVRVGGSSVLHRFHPEPYGLEDDQRS  
 MGYDDLDYGMMSDYGTARRTGTPSDPRRRLRSYEDMIGEEVPSDQYYWAPLAQHER  
 GSLASLDLSLRKGCGPPPNWRQPELPEVIAMLGFRLDAVKSAAAAYLQHLCYRNDKVKT  
 DVRKLKGIPVLVGLLDHPKKEVHLGACGALKNISFGRDQDNKIAIKNCGVPAVLVRLRK  
 ARDMDLTEVITGTLWNLSSHDSIKMEIVDHALHALTDEVIIPHSGWEREPNEDCKPRHIE  
 WESVLTNTAGCLRNVSSERSEARRKLRECDGLVDALIFIVQAEIGQKDSDSKLVENCVC  
 LLRNLSYQVHREIPQAERYQEAAPNVANNTGPHAASCFGAKKGKGKKPIEDPANDTV  
 FPKRTSPARGYELLFQPEVVRIYISLLKESKTPAILEASAGAIQNLCAWRWTYGRYIRSAL  
 RQEKALSAIADLLTNEHERVVKAASGALRNLAVDARNKELIGKHAIPNLVKNLPGQQQN  
 SSWNFSEDTVISILNTINEVIAENLEAAKKLRETQGIEKLVLINKSGNRSEKEVRAAALVLQ  
 TIWGYKELRKPLEKEGWKKSDFQVNLNNASRSQSSHYSYDDSTLPLIDRNQKSDKKPDR  
 EEIQMSNMGSNTKSLDNNYSTPNERGDHNRTLDRSGDLGDMEPLKGTTPLMQDEGQE  
 SLEEELDVVLVLDDEGGQVSYPSMQKI

SEQ ID No: 70

MCRIAGALRTLLPLLALLQASVEASGEIALCKTGFPEDVYSAVLSKDVGQPLLNVKF  
 SNCNGKRKVQYESSEPADFKVDEDGMVYAVRSFPLSSEHAKFLIYAQDKETQEKWQV  
 AVKLSLKPTLTEESVKESAEEIVFPRQFSKHSGHLQRQKRDWVIPPINLPENSRGPF

QELVRIRSDRKNLRLYSVTGPGADQPPTGIFIINPISGQLSVTKPLDREQIARFHLRAH  
 AVDINGNQVENPIDIVINVIDMNDNRPEFLHQVWNGTVPEGSKPGTYVMTVTAIDADDP  
 NALNGMLRYRIVSQAPSTPSNMFTINNETGDIITVAAGLDREKVQQYTLIIQATDMEGN  
 PTYGLSNTATAVITVTDVNNDNPPEFTAMTFYGEVPENRVDIIVANLTVTDKDQPHTPAW  
 NAVYRISGGDPTGRFAIQTDPNSNDGLTVVKPIDFETNRMFVLTVAEENQVPLAKGIQ  
 HPPQSTATSVTVIDVNENPYFAPNPKIIRQEEGLHAGTMLTTAQDPDRYMQQNIRY  
 TKLSDPANWLKIDPVNGQITIAVLDRESPNVNNIYNATFLASDNGIPPMMSGTGTQIYL  
 LDINDNAPQVLPQEAETCETPDPPNSINITALDYDIDPNAGPFAFDLPLSPVTIKRNWTITRL  
 NGDFAQLNLKIKFLEAGIYEVPIITDSGNPPKSNISILRVKVCQCDNSGDCTDVDRIVGAG  
 LGTGAIIAILLCIIILLILVLMFVWWMKRRDKERQAKQLLIDPEDDVRDNILKYDEEGGGEED  
 QDYDLSQLQQPDTVEPDAIKPGIRRMDERPIHAEPQYPVRSAAPHPGDIGDFINEGLK  
 AADNDPTAPPYDSLLVFDYEGSGSTAGSLSSLNSSSSGGEQDYDYLNDWGPRFKKLA  
 DMYGGGDD

SEQ ID No: 71

MPQLNGGGGDDLGANDELISFKDEGEQEEKSESSAERDLADVVKSSLVNESETNQN  
 SSSDSEAERRPPPRSESFRDKSRESLEEAAKRQDGGLFKGPPYPGYPFIMIPDLTSPYL  
 PNGSLSPARTLHFQSGSTHYSAYKTIEHQIAVQYLQMKWPLLDVQAGSLQSRQALKD  
 ARSPSPAHIHSNKVPPVQHPHHVPLTPLITYSNEHFTPQGNPPPQHLPADVDPKTGIPRPP  
 HPPDISPYYPLSPGTVGQIPHPLGWLPQQGPVYPITTGGFRHPYPTALTNASMSRF  
 PPHMVPPHHTLHTTGIPHPAIVPTVKQESSQSDV GSLHSSKHQDSKKEEEKKKPHIKK  
 PLNAFMLYMKEMRAKVAECTLKESAAINQILGRRWHALSREEQAKYYELARKERQLH  
 MQLYPGWSARDNYGKKKKRKRDQKQPGTNEHSECFLNPCLSLPPITDLSAPKKCRARF  
 GLDQQNNWCPCRRKKCVRYIQGEGSCLSPPSDGSLLDSSPPSPNLLGSPPRDAK  
 SQTEQTQPLSLSLKPDPLAHLSSMMPPPALLAEATHKASALCPNGALDLPPAALQPAA  
 PSSSIAQPSTSSLHSHSSLAGTQPQPLSLVTKSLE

SEQ ID No: 72

MEDCNVHSAASILASVKEQEAFERLTRALEQERRHVALQLERAQQPGMVSGGMGSG  
 QPLPMAWQQQLVLQEQQSPGSQASLATMPEAPDVLEETVTVEEDPGPTPTSHVSIVTSEDG  
 TTRRTETKVTKTVKTVTTRTVRQVPVGPDPGLPLLDGGPPPLGPFAVGALDRHFLLRGGG  
 PVATLSRAYLSSGGGFPEGPEPRDSPSYGSLSRGLGMRPPRAGPLGPQGDGCFTLP  
 GHREAFPGPEPGPPGGRSLPERFQAEPYGLEDDTRSLAADDEGGPELEPDYGTATR  
 RRPECGRGLHTRAYEDTADDGELADERPAFPMVTAPLAQPERGSMGSLDRLVRRSP

SVDSARKEPRWRDPELPEVLAMLRHPVDPVKANAAAYLQHLCFENEGVKRRVRQLRG  
 LPLLVALLDHPRAEVRRRACGALRNLSYGRDTDNKAAIRDCGGVPALVRLRAARDNEV  
 RELVTGTLWNLSSYEPLKMWIIDHGLQTLTHEVIVPHSGWEREPNEDSKPRDAEWTTF  
 KNTSGCLRNVSSDGAEARRRLRECEGLVDALLHALQSAVGRKDTDNKSVENCVCIMRN  
 LSYHVHKEVPGADRYQEAEPGPLGSAVGSQRDRDDASCFGKKAKEWFHQGKKD  
 GEMDRNFDTLDLPKRTEAKGFELLYQPEVVRLYLSLLTESRNFTLEAAAGALQNL  
 GNWMWATYIRATVRKERGLPVVELLQSETDKVVRAVIALRNLSLDRRNKDLIGSYAM  
 AELVRNVRNAQAPPRPGACLEEDTVAVLNTIHEIVSDSLDNARSLLQARGVPALVALV  
 ASSQSvreakaashvLQTVWSYKELRGTQKDGWTKARFQSAAATAKGPKGALSPGG  
 FDDSTLPLVDKSLEGEKTGSRDVIPMDALGPDGYSTVDRRERRPRGASSAGEASEKEP  
 LKLDPSRKAPPPGPSRPAVRLVDAVGDAKPQPVDSWV

SEQ ID No: 73

MSTETELQVAVKTSACKDSRKKGQDRSEATLIKRFKGEGVRYKAKLIGIDEVSAARGDK  
 LCQDSMMKLKGVVAGARSKGEHKQKIFLTISFGGIKIFDEKTGALQHHHAVHEISYIAKDI  
 TDHRAFGYVCGKEGNHRFVAIKTAQAAEPVILDRLDFQLIYELKQREELEKKAQKDKQ  
 CEQAVYQTILEEDVEDPVYQYIVFEAGHEPIRDPETEENIYQVPTSQKKEGVYDVPKSQ  
 PNSQPLEDFESRFAAATPNRNLMSDFDELLEATKVSATQLELFGDMSTPPDITSPPPTP  
 ATPGDAFLPSSSQTLPGSADVFGSMSFGTAAVPSGYVAMGAVLPSFWGQQPLVQQQI  
 AMGAQPPVAQVIPGAQPIAWGQPGFPATQQAWPTVAGQFPPAAFMPQTVMPLAAA  
 MFQGPLTPLATVPGTNDSARSSPQSDKPRQKMGKESFKDFQMVPQPPVPSRKPDQPS  
 LTCTSEAFSSYFNKVGVAQDTDDCDDFDISQLNLTPVTSTPSTSPPTPAPRQSSPSK  
 SSASHVSDPTADDIFEEGFESPSKSEEQEAPDGSQASSTDPFGEPSGEPSGDNISPQ  
 DGS

SEQ ID No: 74

MPGPASPAARGLSRRPGQQPLPLLLLPLLLLLRAQPAIGSLAGGSPGAAEAPGSAQVAGL  
 CGRLTLHRDLRTGRWEPPDPQRSRRCLRDPQRVLEYCRQMYPELQIARVEQATQAIPM  
 ERWCGGSRSRGSCAHPHHQVVPFRCLPGEFVSEALLVPEGCRFLHQERMDQCESSTR  
 RHQEAEACSSQGLILHGSGMLLPCGSDRFRGVEYVCCPPPGBTDPSGTAVGDPSTR  
 SWPPGSRVEGADEEEEEESFPQPVDDYFVEPPQAEAAAETVPPPSSHTLAVVGKVTP  
 PRPTDGVDIYFGMPGEISEHEGFLRAKMDLEERRMRQINEVMREWAMADNQSKNLPK  
 ADRQALNEHFQSIQLTLEEQVSGERQRLVETHATRVIALINDQRRAALEGFLAALQADPP  
 QAERVLLALRRYLRAEQKEQRHTLRHYQHVAADVPEKAQQMRFQVHQLQVIEERVN

QSLGLLDQNPHLAQELRPQIQELLHSEHLGPSELEAPAPGGSSEDKGLQPPDSKDDT  
 PMTLPKGSTEQDAASPEKEKMNPLEQYERKVNASVPRGFPHSSEIQRDELAPAGTGV  
 SREAVSGLLIMGAGGGSLIVLSMLLLRRKKPYGAISHGVVEVDPMLTLEEQLRELQRH  
 GYENPTYRFLEERP

SEQ ID No: 75

MPRLKESRSHESSLSPSSAVEALDLSMEEEVVIKPVHSSILGQDYCFEVTTSSGSKCFS  
 CRSAAERDKWMENLRRAVHPNKDNNSRRVEHILKLWIEAKDLPACKYLCELCLDDVL  
 YARTTGKLKTDNVFWGEHFEFHNLPLRTVTVHLYRETDKKKKERNSYLGLVSLPAAS  
 VAGRQFVEKWYPVTPNPKGGKGPGPMIRIKARYQTITILPMEEMYKEFAEHITNHYLGL  
 CAALEPILSAKTKEEMASALVHILQSTGKVKDFTLMMSEVDRCGDNEHLIFRENTLAT  
 KAIIEEEYLKLVGQKYLQDALGEFIKALYESDENCEVDPSKCSAADLPEHQGNLKMCCALA  
 FCKIINSYCVFPRELKEVFASWRQECSSRGRPDISERLISASLFLRFLCPAIMSPSLFNLL  
 QEYPDDRTARTLTLIAKVTQNLANFAKFGSKEEYMSFMNQFLEHEWTNMQRFLLEISNP  
 ETLSNTAGFEGYIDLGRELSSLHSLLWEAVSQLEQSIVSKGPLPRILRDVHTALSTPGS  
 GQLPGTNDLASTPGSGSSSISAGLQKMWENDLSGLIDFTRLPSPTPENKDLFFVTRSSG  
 VQPSPARSSSYSEANEPEDLQMANGGKSLSMVDLQDARTLDGEAGSPAGPDVLPTDGQ  
 AAAAQLVAGWPARATPVNLAGLATVRRAGQTTPGTSEGAPGRPQLLAPLSFQNPVY  
 QMAAGLPLSPRGLGDSGSEGHSSLSSHSNSEELAAAALKGSFSTAEEELARRPGELAR  
 RQMSLTEKGQQPTVPRQNSAGPQRRIDQPPPPPPPPAPRGRTPPNLLSTLQYPRP  
 SSGTLASASPDWVGPPSTRLRQQSSSSKGDSPELKPRAVHKQGPSPVSPNALDRTAAW  
 LLTMNAQLLEDEGLGPDPHRDRRLRSKDELSQAEKDLAVLQDKLRISTKKLEEYETLFK  
 CQEETTQKLVLEYQARLEEGERRRQQEDKDIQMKGIIISRLMSVEEELKKDHAEMQA  
 AVDSKQKIIDAQEKRISLDAANARLMSALTQLKERYSMQARNGISPTNPTKLQITENGE  
 FRNSSNC

SEQ ID No: 76

ADIISTVEFNHSGELLATGDKGGRVVIFQQEQENKIQSHSRGEYNVYSTFQSHEPEFDY  
 LKSLEIEEKINKIRWLPQKNAAQFLLSTNDKTIKLWKISERDKPEGYNLKEEDGRYRDP  
 TTVTTLRVSTKKMSQIVLVFILYSPNPEQSLNRNNYSLSPSQPMMDLMVEASPRRIIFAN  
 AHTYHINSISINSDYETYLSDADDRINLWHEITDRSFNIVDIKPANMEELTEVITAAEFHPN  
 SCNTFVYSSSKGTIRLCDMRASALCDRHSKLFEEPEDPSNRSFFSEIISISDVKFHSG  
 RYMMTRDYLSVKIWDLNMENTRPVETYQVHEYLRSKLCSLYENDCIFDKFELYCLFHSVV

MTGSYNFFRMFDRNTKRDITLEASRENNPRTVLKPRKVCASGKRKKDEISVDSLDFN  
KKILHTAWHPKENIIAVATTNNLYIF

SEQ ID No: 77

MELRVGNRYRLGRKIGSGSGDIYLGTIAAGEEEVAIKLECVKTGHPLHIESKIYKMMQ  
GGVGIPTIRWCGAEGDYNVMVMELLGPSLEDLFNFCSRKFSLKTVLLLADQMISRIEYIH  
SKNFIHRDVKPDMFLMGLGKKGNLVYIIDFGLAKKYRDAARTHQHIPYRENKNLTGTARYA  
SINTHLGIEQSRRDDLES LGYVLMYFNLGSLPWQGLKAATKRQKYERISEKKMSTPIEVL  
CKGYPSEFATYLNFCRSLRFDDKPDYSYLRQLFRNLFRQGFSYDYVFDWNMLKFGAS  
RAADDAAERERRDREERLHSRNPATRGLPSTASGRRLRGQTQEVAAPPTPLTPTSHTANTS  
PRPVSGMERERKVSMRLHRGAPVNISSSDLTGRQDTSRMSTSQIPGRVASSGLQSVV  
HR

SEQ ID No: 78

MAGNF DSEERSSWYWGRLSRQEAVALLQGQRHGVFLVRDSSTSPGDYVLSVSENSR  
VSHYIINSSGPRPPVPPSPAQPPPGVSPSRLRIGDQEFDSPALLEFYKIHYWDTTLIEP  
VSRSRQSGVILRQEEAEYVRALFDNGNDEEDLPFKKGDLRIRDKPEEQWWNAEDS  
EGKRG MIPV PVYVEKYRPASASVSALIGGNQEGSHPQPLGPPEPGPYAQPSVNTPNL  
QNGPIYARVIQKRVPNAYDKTALALEVGELVKVTINVSGQWE GG CNGKRGHFPFTHV  
RLLDQQNPDED FS

SEQ ID No: 79

MGC VQCKDKEATKLTEERDGSLNQSSGYRYGTDPTPQHYP SFGVTSIPNYNNFH AAG  
GQGLTVFGGVNSSHTGTLRTRGGTGVTLFVALYDYEARTEDDL SFHKGEKFQILNSST  
KKGGKEGPEPQEIRFAGRS DLLEG NHVVD CRLVEGSADT QWMSEPQRHIHGLPDVNG  
KRWYFGKLGRKDAERQLLSFGNPRGTFLIRESETTKGAYSL SIRDWDDMKGDHV KHYK  
IRKLDNGGYYITTRAQFETLQQLVQHY SERAAGLCCRLVVPCHKGMPRLT DLSVKT KDV  
WEIPRESLQLIKRLGNGQFGEVWMGTWNGNTKVAIKTLKPGTMS PESFLEE AQIMKKLK  
HDKLVQLYAVVSEEPIYIVTEYMNKG SLLDFLKDGEGRALKLPNLVDMAAQVAAGMAYI  
ERMNYIHRDLRSANILVGNGLICKIADFG LARLIEDNEY TARQGAKFPIKWT APEAALYGR  
FTIKSDVWSFGILLTELVTKGRVPY PG MNNREVLEQVERGYRMPCPQDCPISLHELMIH  
CWKKDPEERPTFEYLQSFLEDYFTATEPQYQPGENL

SEQ ID No: 80

MSVVG LDVG SQSC YIAVARAGGIETIANEFS DRCTPSVISFGSKNRTIGVAAKNQQITHA  
 NNTVS NF KRF HGRAFNDPFIQKEKENLSYDLVPLNGGVGIKVMYMGEEHLFSVEQITA  
 MLLTKLKETAENSLKKPVTD C VISVPSFFTDAERRSVLDAAQIVGLNCLRLMNDMTAVAL  
 NYGIYKQD LPSLDEKPRI VVFVDMGHSAFQVSACAFNKGKLVLGTA FDPFLGGKNFDE  
 KLVEHFCAEFKTKYKLD A SKIR ALLR LYQECEKLKLMSSNSTDPLNIECFMNDKDVS  
 GKMNR SQF EELCAELLQKIEVPL YSLLEQTHLKV EDV S AVEIVGGATRIPAVKERIAKFFG  
 KDISTLN ADEAVARGCALQC AILSPA FKVREFS VTDAV PFPISLIWNHDSEDTEGVHEV  
 FSRNHAAPFSKVLTFLRRGPFELEAFYSDPQGV PYPEAKIGRFVVQNVS AQKDGEKSR  
 VKVKVRVNTHGIFTISTASMVEKVPTEENEMSSEADMECLNQRPPENPD TDKNVQQDN  
 SEAGTQPQVQTDAQQTSQSPPSPELTSEENKIPDADKANEKKVDQPPEAKPKIKV  
 VELPIEANLVWQLGKD LNMYIETEGKMIMQDKLEKERND A KNAVEEYVYEFRDKLCGP  
 YEKFICEQDHQNFLRLLTETEDWLYEEGEDQAKQAYVDKLEELMKIGTPVKVRFQEAE  
 RPKMFEELGQRLQHYAKIAADFRNKDEKYNHIDESEM KKVEKSVNEVM EWMNNVMNA  
 QAKKSLDQDPVVRAQEIKTKIKELNN TCEPVVTQPKPKIESPKLERTPNGPNIDKKEEDL  
 EDKNNFGAEPPHQNGECYPNEKNSVNMDLD

SEQ ID No: 81

MSVVG LDVG SQSC YIAVARAGGIETIANEFS DRCTPSVISFGSKNRTIGVAAKNQQITHA  
 NNTVS NF KRF HGRAFNDPFIQKEKENLSYDLVPLNGGVGIKVMYMGEEHLFSVEQITA  
 MLLTKLKETAENSLKKPVTD C VISVPSFFTDAERRSVLDAAQIVGLNCLRLMNDMTAVAL  
 NYGIYKQD LPSLDEKPRI VVFVDMGHSAFQVSACAFNKGKLVLGTA FDPFLGGKNFDE  
 KLVEHFCAEFKTKYKLD A SKIR ALLR LYQECEKLKLMSSNSTDPLNIECFMNDKDVS  
 GKMNR SQF EELCAELLQKIEVPL YSLLEQTHLKV EDV S AVEIVGGATRIPAVKERIAKFFG  
 KDISTLN ADEAVARGCALQC AILSPA FKVREFS VTDAV PFPISLIWNHDSEDTEGVHEV  
 FSRNHAAPFSKVLTFLRRGPFELEAFYSDPQGV PYPEAKIGRFVVQNVS AQKDGEKSR  
 VKVKVRVNTHGIFTISTASMVEKVPTEENEMSSEADMECLNQRPPENPD TDKNVQQDN  
 SEAGTQPQVQTDAQQTSQSPPSPELTSEENKIPDADKANEKKVDQPPEAKPKIKV  
 VELPIEANLVWQLGKD LNMYIETEGKMIMQDKLEKERND A KNAVEEYVYEFRDKLCGP  
 YEKFICEQDHQNFLRLLTETEDWLYEEGEDQAKQAYVDKLEELMKIGTPVKVRFQEAE  
 RPKMFEELGQRLQHYAKIAADFRNKDEKYNHIDESEM KKVEKSVNEVM EWMNNVMNA  
 QAKKSLDQDPVVRAQEIKTKIKELNN TCEPVVTQPKPKIESPKLERTPNGPNIDKKEEDL  
 EDKNNFGAEPPHQNGECYPNEKNSVNMDLD

SEQ ID No: 82

MAAADGDDSLYPIAVLIDELRNEDVQLRLNSIKKLSTIALALGVERTRSELLPFLTDTIYDE  
 DEVLLALAEQLGTFTTLVGGPEYHCLLPPLESLATVEETVVRDKAVESLRAISHEHSPS  
 DLEAHFVPLVKRLAGGDWFTSRTSACGLFSVCYPRVSSAVKAELRQYFRNLCSDDT.PM  
 VRRAAAASKLGEFAKVLELDNVKSEIIPMFSNLASDEQDSVRLLAVEACVNIAQLLPQEDL  
 EALVMPTLRQAAEDKSWRVRYMVADKFTELQKAVGPEITKTDLVPAFQNLMKDCEAEV  
 RAAASHKVKEFCENLSADCRENVIMSQILPCIKEVLSDANQHVKSALASVIMGLSPILGK  
 DNTIEHLLPLFLAQLKDECPEVRLNIISNLDCVNEVIGIRQLSQSLLPAIVELAEDAKWRVR  
 LAIIEYMPPLLAGQLGVEFFDEKLNLCMAWLVDHVYAIRAATSNKKLVEKFGKEWAHA  
 TIIPKVLAMSGDPNYLHRMTTFCINVSEVCGQDITTKHMLPTVLRMAGDPVANVRFNV  
 AKSLQKIGPILDNSTLQSEVKPILEKLTQDQDVKYFAQEALT VLSLA

SEQ ID No: 83

MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGE GG  
 GPEPGPANAKWLKEGQNQLRRAATAHRDQRNRVTLTLAEEASQEPEMAPLGPKGLIHL  
 YSELELSAHNAANRGLRGPGLIISTQEQQPDEGEEKAAAGEAEEEEEDDDDEEEEEDLS  
 SPPGLPEPLESVEAPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
 SYGSPEDTDSFWNPNAFETSDLPAGWMRVQDTSGTYYWHIPTGTTQWEPPGRASP  
 SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFFPAQS  
 LSPEPLPQEEEKLPPRNTNPGIKCFAVRSLGWVEMTEELAPGRSSVAVNNCIRQLSYH  
 KNNLHDPMSSGGWGEGKDLLLQLEDETLKVEPQSQALLHAQPIISIRVGWGVGRDSGRE  
 RDFAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICSKIMAERRNARCLVNGLSDLHS  
 KLVDPFQVEFPAPKNELVQKFQVYLYGNVPVAKPGVDVINGALESVLSSSREQWT  
 PSHVSVAPATLTILHQQTTEAVLGECRVRFLSFLAVGRDVHTFAFIMAAGPASFCCHMF  
 CEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWTVRRGVQS  
 LWGSLKPKRLGAHTP

SEQ ID No: 84

MSVPSSLSQSAINANSHGGPALSPLPLHAAHNQLLNAKLQATAVGPKDLRSAMGE GG  
 GPEPGPANAKWLKEGQNQLRRAATAHRDQRNRVTLTLAEEASQEPEMAPLGPKGLIHL  
 YSELELSAHNAANRGLRGPGLIISTQEQQPDEGEEKAAAGEAEEEEEDDDDEEEEEDLS  
 SPPGLPEPLESVEAPRPQALTDGPREHSKSASLLFGMRNSAASDEDSSWATLSQGSP  
 SYGSPEDTDSFWNPNAFETSDLPAGWMRVQDTSGTYYWHIPTGTTQWEPPGRASP  
 SQGSSPQEESQLTWTGFAHGEGFEDGEFWKDEPSDEAPMELGLKEPEEGTLTFFPAQS  
 LSPEPLPQEEEKLPPRNTNPGIKCFAVRSLGWVEMTEELAPGRSSVAVNNCIRQLSYH

KNNLHDPMGGWGEKDLLQLEDETLKLVEPQSQALLHAQPIISIRVGVRDSGRE  
 RDFAYVARDKLTQMLKCHVFRCEAPAKNIATSLHEICSKIMAERRNARCLVNGLSLDHS  
 KLVDPFQVEFPAPKNELVQKFQVYLYGNVPVAKPGVDVINGALESVLSSSREQWT  
 PSHVSVAPATLTLHQQTTEAVLGECRVRFLSFLAVGRDVHTFAFIMAAGPASFCCHMFW  
 CEPNAASLSEAVQAACMLRYQKCLDARSQASTSCLPAPPAESVARRVGWTVRRGVQS  
 LWGSLKPRLGAHTP

SEQ ID No: 85

MDAEFRHDSGYEVHHQKLVFFAEDVGSNKGAIIGLMVGGVIATVIVITVMLKKKQYTSI  
 HHGVVEVDAAVTPEERHLSKMQQNGYENPTYKFFEQMQN

SEQ ID No: 86

MDFQHRPGGKTGSGVASSSESNRDRRERLRQLALETIDINKDPYFMKNHLGSYECKL  
 CLTLHNNEGSYLAHTQGKKHQTNLARRAAKEAKEAPAQPAPEKVKVEVKKFVKIGRPG  
 YKVTKQRDSEMGQQSLLFQIDYPEIAEGIMPRHRFMSAYEQRIEPPDRRWQYLLMAAE  
 PYETIAFKVPSREIDKAEGKFWTHWNRETQFFLQFHFKMEKPPAPPSPAGPPGVKR  
 PPPPLMNGLPPRPLPESLPPPPGGLPLPPMPPTGPAPSGPPGPPQLPPPAPGVHPP  
 APVVHPPASGVHPPAPGVHPPAPGVHPPAPGVHPPPTSGVHPPAPGVHPPAPGVHPPA  
 PGVHPPAPGVHPPAPGVHPPPSAGVHPQAPGVHPAAPAVHPQAPGVHPPAPGMHPQ  
 APGVHPQPPGVHPSAPGVHPQPPGVHPSNPGVHPPTPMPPMLRPLPSEGPGNIPPP  
 PPTN

SEQ ID No: 87

MLGKDYMLAIILVNCDDDLWGDHSLEVEAGLPPGWRKIHDAAGTYYWHVPSGSTQWQ  
 RPTWELGDAEDPGTGTEGIWGLRPPKGRSFSSLESSLDRSNLSWYGGESYIQSMEP  
 GAKCFAVRSLGWVEVPEEDLAPGKSSIAVNNCIQQLAQTRSRSQPPDGAWGEGQNML  
 MILKKDAMSLVNPLDHSLIHCQPLVHIRVGVGSSKGRFYPSPISAPARDFAFVASDKD  
 SCMLKCHVFCCDVPAKAIASALHGLCAQILSERVEVSGDASCCSPDPISPEDLPRQVEL  
 LDAVSQAAQKYEALYMGTLPVTKAMGMDVLNEAIGTLTARGDRNAWVPTMLSVDL  
 MTAHPIQAEASTEEPLWQCPVRLVTFIGVGRDPHTFGLIADLGRQSFQCAFWCQPH  
 AGGLSEAVQAACMVQYQKCLVASAARGKAWGAQARARLRLKRTSSMDSPGGPLPL  
 LKGGVGGAGATPRKRGVFSFLDAFRLKPSLLHMP

SEQ ID No: 88

MEVDGTPRRGGCKMPLPVQVFNLQGAVEPMQIDVDPQEDPQNAPDVNYVVENPSLDL  
 EQYAASYSGLMRIERLQFIADHCPTLRVEALKMALSFVQRTFNVDMYEEIHRKLSEATR  
 ELQNAPDAIPESGVVEPPALDTAWVEATRKKALLKLEKLDLKNYKGNSIKESIRRGHDD  
 LGDHYLDCGDLASNALKCYSRARDYCTSAKHVINMCLNVIVSVYLQNWSHVLSYVSKA  
 ESTPEIAEQRGERDSQTQAILTKLCAAGLAELAARKYKQAACLLASFDHCDFPELLS  
 PSNVAIYGGLCALATFDRQELQRNVISSSSFKLFLELEPQVRDIIFKFYESKYASCLKMLD  
 EMKDNLLLDMYLAPHVRTLYTQIRNRALIQYFSPYVSADMHRMAAFNTTVAALEDELT  
 QLILEGLISARVDSHSKILYARDVDQRSTFEKSLLMGKEFQRRAKAMMLRAAVLRNQIH  
 VKSPPREGSQGELTPANSQSRMSTM

SEQ ID No: 89

MSDMEDDFMCDDEEDYDLEYSEDSNSEPNVDLENQYYNSKALKEDDPKAALSSFQKV  
 LELEGEKGEWGFKALKQMIKINFKLTNFPEMMNRYKQLLTYIRSAVTRNYSEKSINSILD  
 YISTSKQMDLLQEfyETTLEALKDAKNDRWFKTNTKLGKLYLEREEYGKLQKILRQLHQ  
 SCQTDDGEDDLKKGTQLLEIYALEIQtyTAQKNNKKLKALYEQSLHIKSAIPHPLIMGVIR  
 ECGGKMHREGEFEKAHTDFFEAFKNYDESGSPRTTCLKYLVLANMLMKSGINPFDS  
 QEAKPYKNDPEILAMTNLV SAYQNN DITEFEKILKTNHSNIMDDPFIREHIEELLRNIRTQV  
 LIKLIKPYTRIHIPFISKELNIDVADVESLLVQCILDNTIHGRIDQVNQLLELDHQKRGGARY  
 TALDKWTNQLNSLNQAVVSKLA

SEQ ID No: 90

MAAAVRQDLAQLMNSSGSHKDLAGKYRQILEKAIQLSGAEQLEALKAFVEAMVNENVS  
 LVISRQLLTDFTCHLPNLPDSTAKEYHFTLEKIQPRVISFEEQVASIRQHLASIYEKEEDW  
 RNAAQVLVGIPLETGQKQYNVDYKLETYLKIA RLYLEDDDPVQAEAYINRASLLQNESTN  
 EQLQIHYKVCYARVLDYRRKFIEAAQRYNELSYKTIVHESERLEALKHALHCTILASAGQ  
 QR SRMLATLFKDERCQQLAAYGILEKMYLDRIIRGNQLQEFAAMLMPHQKATTADGSSI  
 LDRAVIEHNLLSASKLYNNITFEELGALLEIPA AKAEKIASQMITEGRMNGFIDQIDGIVHF  
 ETREALPTWDKQIQSLCFQVNNLLEKISQTAPEWTAQAMEAQMAQ

SEQ ID No: 91

MAASGSGMAQKTWELANNMQEAQSIDEIYKYDKKQQQEILAANLGTKDHHYFKYCKIS  
 ALALLKVMVMHARSGGNLEVMGLMLGV DGETMIIMDSFALPVEGTETRVNAQAAAYEY  
 MAAYIENAKQVGRLENAIGWYHSHPGYGCWLSGIDVSTQMLNQQFQEPPVAVVIDPTR  
 TISAGKVNGLGAFRTYPKGYKPPDEGPSEYQTIPNKIEDFGVHCKQYYALEVSYFKSSL

RKLLELLWNKYWVNTLSSSSLLTNADYTTGQVFDLSEKLEQSEAQLGRGSFMLGLETH  
DRKSEDKLAKATRDSCKTTIEAIHGLMSQVIKDKLFNQINIS

SEQ ID No: 92

MAAAAAAAAATNGTGGSSGMEVDAAVPSVMACGVTGSVSVALHPLVILNISDHWIRM  
RSQEGRPVQVIGALIGKQEGRNIEVMNSFELLSHTVEEKIIIDKEYYYTKEEQFKQVFKEL  
EFLGWYTTGGPPDPSDIHVHKQVCEIIESPFLKLNPMTKHTDLPVSVFESVIDIINGEAT  
MLFAELTYTLATEEAERIGVDHVARMTATGSGENSTVAEHLIAQHSAIKMLHSRVKLILEY  
VKASEAGEVPFNHEILREAYALCHCLPVLSTDKFKTDFYDQCNDVGLMAYLGTITKTCN  
TMNQFVNKFNVLYDRQGIGRRMRGLFF

SEQ ID No: 93

MSAEVKVTGQNQEQQFLLLAKSAKGAAALATLIHQVLEAPGVYVGELLDMPNVRELAESD  
FASTFRLLTVFAYGTYADYLAEARNLPLLTEAQKNKLRHLSVVTAAKVKCIPYAVLLEAL  
ALRNVRQLEDLVIEAVYADVLRGSLDQRNQRLEV DYSIGRDIQRQDLSAIARTLQEWCV  
GCEVVLSGIEEQVSRANQHKEQQQLGLKQQIESEVANLKKTIKVTTAAAAAATSQDPEQH  
LTELRREPAPGTNQRQPSKKASKGKGLRGSAKIWSKSN

SEQ ID No: 94

MPVAVMAESAFSFKLLDQCENCQELEAPGGIATPPVYGQLLALYLLHNDMNNARYLWK  
RIPPAIKSANSSELGGIWSVGQRIWQRDFPGIYT TINAHQWSETVQPIMEALRDATRRRAF  
ALVSQAYTSIIADDFAAFVGLPVEEAVKGILEQGWQADSTTRMVLPRKPVAGALDVSFN  
KFIPLSEPAPVPPPIPNEQQLARLTDYVAFLN

SEQ ID No: 95

MLIKVKTLTGKEIEIDIEPTDKVERIKERVEEKEGIPPQQQR LIYSGKQMNEKTAADYKIL  
GGSVLHLVLALRGGGGLRQ

SEQ ID No: 96

MAAAMDVDTSPGTNSGAGKKRFEVKKWNAVALWA WDIVVDNCAICRNHIMDLCIECQA  
NQASATSEEECTVAWGVCNHAFHFHCISRWLKTRQVCPLDNREWEFQKYGH

SEQ ID No: 97

MDADMDYERPNVETIKCVVVGDNAVGKTRLICARACNTTLTQYQLLATHVPTVWAIDQY  
 RVCQEVLERSRDVVDESVSLRLWDTFGDHDKDRRFAYGRSDVVLCFSIANPNSLNH  
 VKSMWYPEIKHFCPRTPVILVGCQLDLRYADLEAVNRARRPLARPIKRGDILPPEKGREV  
 AKELGLPYYETSVDQFGIKDVFDNAIRALAISRRHLQFWKSHLKKVQKPLLQAPFLPPK  
 APPPKIPECPMTNEAACLLDNPLCADVLFILQDQEHIHRIYLATSSSKFYDLFLM  
 ECEESPNGSEGACEKEKQSQRDFQGRILSVDPEEEEREEGPPRIPQADQWKSSNKLVEA  
 LGLEAEGAVPETQTLTGWSKGFIGMHREMNVNPISKRMGPMTVVRMDASVQPGPFRT  
 LLQFLYTGQLDEKEKDLVGLAQIAEVLEMFDLRMMVENIMNKEAFMNQEITKAFHVRKA  
 NRIKECLSKGTFSVTFKLDDGAISAHKPLLICSEWMAAMFGGSFVESANSEVYLPNIN  
 KISMQAVALDYLYTKQLSPNLDDPLELIALANRFCLPHLVALAEQHAVQELTKAATSGVGI  
 DGEVLSYLELAQFHNAHQLAACWCLHHICTNYNSVCSKFRKEIKSKSADNQEYFERHRW  
 PPWYLKEEDHYQRVKREREKEDIALNKHRSRRKWCWNSSPAVA

SEQ ID No: 98

ACSAGRDFVFLTLEATPSHVVSRLMDSDMDYERPNVETIKCVVVGDNAVGKTRLICARA  
 CNATLTQYQLLATHVPTVWAIDQYRVCQEVLERSRDVVDDVSVSLRLWDTFGDHDKDR  
 RFAYGRSDVVVLCSIANPNSLHHVKTMWYPEIKHFCPRAPVILVGCQLDLRYADLEAV  
 NRARRPLARPIKPNEILPPEKGREVAKELGIPYYETSVAQFGIKDVFDNAIRALAISRRH  
 LQFWKSHLRNVQRPLLQAPFLPPKPPPPPIVVPDPSSSEECPAHLLLEDPLCADVILVLQ  
 ERVRIFAHKIYLSTSSSKFYDLFLMDLSEGELGGPSEPGGTHPEDHQGHSDQHHHHHH  
 HHGRDFLLRAASFDCESVDEAGGSGPAGLRASTDGILRGNGTGYLPGRGRVLSS  
 WSRAFVSIQEEMAEDPLTYKSRLMVVVKMDSSIQPGPFRAVLKYLYTGELDENERDLM  
 HIAHIAELLEVFDLRMMVANILNNEAFMNQEITKAFHVRRTNRVKECLAKGTFSDVTFILD  
 DGTISAHKPLLISSCDWMAAMFGGPVESSTREVVFPTSKSCMRNAVLEYLYTGGMFTSS  
 PDLDMDMKLIILANRLCLPHLVALTEQYTVTGLMEATQMMVDIDGDVLVFLEAQFHCAQ  
 LADWCLHHICTNYNNVCRKFPRDMKAMSPENQEYFEKHRWPPWYLKEEDHYQRAR  
 KEREKEDYLHLKRQPKRRLFWNSPSSPSSSAASSSSPSSSSAVV

SEQ ID No: 99

KSIVKIRNRMAAETQTLNFGPEWLRALSSGGTSPPPLSPALPKYKLADYRYGREEMLAL  
 FLKDNKIPSDLKDKEFLPILQEEPLPPLALVPFTEEEQRNFMSVNSAAVRLRTGRGGGG  
 TVVGAPRGRSSSRGRGRGRGECGFYQRSFDEVEGVFGRGGGREMHRSQSWEERGD  
 RRFEKPGRKDVGKKNGYYCMYSPVLLGQPLCQGRPNFEEGGPTSVGRKHEFIRSES  
 ENWRIFREEQNGEDEDGGWRLAGSRRDGERWRPHSPDGPRSAGWREHMERRRF

FDFRDRDDERGYRRVRSGSGSIDDDRDSLPEWCLEDAEEEEMGTFDSSGAFLSLKKVQ  
 KEPIPEEQEMDFRPVDEGEECSDSEGHNEEAKEPDKTNKEGEKTDRVGVASEETP  
 QTSSSARPGTPSDHQSQEASQFERKDEPKTEQTEKAEEETRMENSLPAKVPSRGDE  
 MVADVQQPLSQIPSDTASPLLILPPPVPNPSPTLRPVETPVVGAPGMGSVSTEPDDEEG  
 LKHLEQQAEKMVAYLQDSALDDERLASKLQEHRAGVSIPLMHEAMQKWYYKDPQGEI  
 QGPFNNQEMAWEWFQAGYFTMSLLVKRACDESQPLGDIMKMWGRVPFSPGPAPPPH  
 MGELDQERLTRQQELTALYQMQLQYQQFLIQQQYAQVLAQQQKAALSSQQQQQLAL  
 LLQQFQTLKMRISDQNIIPSVTRSVSPDTGSIWELQPTASQPTVWEGGSVWDLPLDTT  
 TPGPALEQLQQLEKAKAAKLEQERREAEMRAKREEEERKRQEELRRQQEEILRRQQEE  
 ERKRREEEELARRKQEEALRRQQREQEIALRRQQEEERQQQEEALRRLEERRREEEE  
 RRKQEELLRKQEEAAKWAREEEEAQRRLEENRLRMEEAARLRHEEEERKRKELEV  
 QRQKELMRQRQQQQEALRRLQQQQQQQLAQMKLPSSSTWGQQSNTTACQSQATL  
 SLAEIQKLEERERERQLREEQRRQQRELMKALQQQQQQQLSGWGNVSKPSGTTK  
 SLLEIQQEEARQMKGQQQQQQHQQPNRARNNTHSNLHTSIGNSVWGSINTGPPNQ  
 WASDLVSSIWSADTKNSNMFWDDAVKEVGPRNSTKNKNNASLSKSVGSRQN  
 KKVEEEKLLKLFQGVNKAQDGFTQWCEQMLHALNTANNLDVPTFVSLKEVESPYEV  
 HDYIRAYLGDTSEAKEFAKQFLERRAKQKANQQRQQQLPQQQQQQPPQQPPQQPQ  
 QQDSVWGMNHSTLHSVQTNQSNNQGSNFEAVQSGKKKKQKMVRADPSLLGFSVN  
 ASSERLNMGEIETLDDY

SEQ ID No: 100

MRLTRCQAALAAAITLNLLVLFYVSWLQHQPRNSRARGPRRASAAGPRVTVLVREFEA  
 FDNAVPELVDSFLQQDPAQPVVAADTLPYPPALPRIPNVRLALLQPALDRPAAASRP  
 ETYVATEFVALVPDGARAEAPGLLERMVEALRAGSARLVAAPVATANPARCLALNVSLR  
 EWTARYGAAPAAPRCDALDGDAVVLLRARDLFNLSAPLARPVGTSFLQTALRGWAVQ  
 LLDLTFAAARQPPLATAHWKAEREGRARRAALLRALGIRLVSWEGGRLEWFGCNKE  
 TTRCFGTVVGDTPAYLYEERWTPPCCLRALRETARYVVGVLLEAGVRYWLEGGSLGA  
 ARHGDIIPWDYDVLGIYLEDVGNCEQLRGAEGSVVDERGFVWEKAVEGDFFRVQYS  
 ESNHLHVDLWPFYPRNGVMTKDTWLDHRQDVFPEHFLQPLVPLFAGFVAQAPNNY  
 RRFLELKFGPGVIENPQYPNPALLSLTGSG

SEQ ID No: 101

HLPKQQRGGVCLGVKSQWQPKLRTGREKIINMHFQAFWLCLGLLFISINADEFMDDDVET  
 EDFEENSEEIDVNESELSSIEKYKTPQPIGEVYFAETFDSGRLAGWVLSKAKKDDMDEEI

SIYDGRWEIEELKENQVPGDRGLVLKSRAKHHAISAVLAKPFIFADKPLIVQYEVNQFDGI  
 DCGGAYIKLLADTDDLILENFYDKTSYIIMFGPDKGEDYKLHFIFRHKHPKTGVFEEKHA  
 KPPDVLDKKFFTDRKTHLYTLVMNPDDTFEVLDQTVVNKGSLLEDVVPPIKPPKEIEDP  
 NDKKPEEWDERAKIPDPSAVKPEDWDESEPAQIEDSSVVVKPAGWLDDEPKFIPDPNAE  
 KPDDWNEDTDGEWEAPQILNPACRIGCGEWKPPMIDNPKYKGVWRPPLVDNPNYQGI  
 WSPRKIPNPDYFEDDHPPFLTSFSALGLELWSMTSDIYFDNFIIICSEKEVADHWAADGW  
 RWKIMIANANKPGVLKQLMAAAEGHPWLWLIYLVTAGVPIALITSFCWPRKVKKHKDT  
 EYKKTDICIPQTKGVLEQEEKEEKAALEKPMDEEEKKQNDGEMLEKEEESEPEEKSEE  
 EIEIIEGQEESNQSNKSGSEDEMKEADESTGSGDGPIKSVRKRRVRKD

SEQ ID No: 102

MRCCHICKLPGRVMGIRVRLSLVVILVLLL VAGALTALLPSVKEDKMLMLRREIKSQGK  
 STMDSFTLIMQTYNRTDLLLKLLNHYQAVPNLHKVIVVWNNGEKA PDELWNSLGPHPPIP  
 VIFKQQTANRMNRNRLQVFPELETNAVLMVDDDTLISTPDLVFAFSVWQQFPDQIVGFVP  
 RKHVSTSSGIYSYGSFEMQAPGSGNGDQYSMVLIGASFFNSKYLELFQRQPAAVHALID  
 DTQNCDDIAMNFIIAKHIGKTSGIFVKPVNMDNLEKETNSGYSGMWHRAEHALQRSYCI  
 NKLVNIYDSMPLRYSNIMISQFGFPYANYKRKI

SEQ ID No: 103

MRCCHICKLPGRVMGIRVRLSLVVILVLLL VAGALTALLPSVKEDKMLMLRREIKSQGK  
 STMDSFTLIMQTYNRTDLLLKLLNHYQAVPNLHKVIVVWNNGEKA PDELWNSLGPHPPIP  
 VIFKQQTANRMNRNRLQVFPELETNAVLMVDDDTLISTPDLVFAFSVWQQFPDQIVGFVP  
 RKHVSTSSGIYSYGSFEMQAPGSGNGDQYSMVLIGASFFNSKYLELFQRQPAAVHALID  
 DTQNCDDIAMNFIIAKHIGKTSGIFVKPVNMDNLEKETNSGYSGMWHRAEHALQRSYCI  
 NKLVNIYDSMPLRYSNIMISQFGFPYANYKRKI

SEQ ID No: 104

MAERRRHKKRIQEVGEP SKEEKAVAKYLRFCPTKSTNM MGHRVDYFIASKAVDCLLD  
 SKWAKAKKGE EALFTTRESVVDYCNRLLKKQFFHRALKVMKMKYDKDIKKEKDKGKAE  
 SGKEEDKKSKKENIKDEKTKEKEKEKKDGEKEESKKEETPGTPKKKETKKFKLEPHDD  
 QVFLDGNEVYVWIYDPVHFKTFVMGLILVIAVIAATLPLWPAEMRVGVYYLSVGAGCFV  
 ASILLAVARCILFLIWLITGGRHHFWFLPNLTADVGFIDSFRPLYTHEYKGPKADLKDE  
 KSETKKQQKSDSEEKSDSEKKEDEEGKVGPNGHGTEGSGGERHSDTDSRREDDRS  
 QHSSGNGNDFEMITKEELEQQTDGDCEEDEEEENDGETPKSSHEKS

SEQ ID No: 105

MGCKGDASGACAAGALPVTGVCYKMGVLVLTWLWFSSVKADSKAITTSLTTKWFST  
 PLLLEASEFLAEDSQEKFWNFVEASQNIGSSDHGTDYSYYHAILEAAFQFLSPLQQNL  
 FKFCLSLRSYSATIQAFQQIAADEPPPEGCNSFFSVHGKKTCESDTLEALLTASERPKP  
 LLFKGDHRYPSSNPESPVVIFYSEIGSEEFNFHRQLISKSAGKINYVFRHYIFNPRKEP  
 VYLSGYGVELAIKSTEYKAKDDTQVKGTEVNTTVIGENDPIDEVQGFLFGKLRLDLHPDLE  
 GQLKELRKHLVESTNEMAPLKVVQLQDLSFQTAARILASPVELAVVMKDLSQNFPKA  
 RAITKTAVSSELRTVEEENQKYFKGTLGLQPGDSALFINGLHMDDLTQDIFSLFDVLRNE  
 ARVMEGLHRLGIEGLSLHNVLKLNIPSEADYAVDIRSPAISWVNNEVDSRYNSWPSS  
 LQELLRPTFPGVIRQIRKNLHNMFIVDPAHETTAELMNTAEMFLSNHIPLRIGFIFVVND  
 SEDVDGMQDAGVAVLRAYNYVAQEVDYHAFQTLTHIYNKVRTGEKVKVEHVVSVLEK  
 KYPYVEVNSILGIDSAYDRNRKEARGYYEQTGVGPLPVVLFNGMPFEREQLDPDELETI  
 TMHKILETTFFFQRAVYLGELPHDQDVVEYIMNQPNVPRINSRILTAERDYLDLTASNN  
 FFVDDYARFTILDSQGKTAAVANSMNYLTGGMSSKEIYDDSFIRPVTFWIVGDFDSPS  
 GRQLLYDAIKHQKSSNNVRISMINNPAKEISYENTQISRAIWAALQTQTSNAAKNFIKMA  
 KEGAAEALAAGADIAEFSVGGMDFLKEVFESSKMDFILSHAVYCRDVLKLKKGQRAV  
 ISNGRIIGPLEDSELFNQDDFHLLENIILKTSGQKIKSHIQLRVEEDVASDLVMKVDALLS  
 AQPKGDPRIEYQFFEDRHSAIKLRPKEGETYFDVVAVVDPVTREAQRALPLLVLAQLIN  
 MNLRVFMNCQSKLSDMPLKSFYRYVLEPEISFTSDNSFAKGPIAKFLDMPQSPLFTLNL  
 NTPESWMVESVRTPYDLDNIYLEEVDSVVAAEYELEYLLLEGHCYDITTGQPPRGLQFT  
 LGTSANPVIVDTIVMANLGYFQLKANPGAWILRLRKGRSEDIYRIYSHDGTDSPPDADEV  
 VIVLNNFKSKIIVKVQKKADMVNEDLLSDGTSENESGFWDASFKWGFTGQKTEEVKQD  
 KDDIINIFSVASGHLYERFLRIMMLSVLKNTKTPVKFWFLKNYLSPTFKEFIPYMANEYNF  
 QYELVQYKWPRLHQQTKEQRIIWGYKILFLDVLFPLVVDKFLVDADQIVRTDLKELRD  
 FNLDGAPYGYTPFCDSRREMDGYRFWKSGYWASHLAGRKYHISALYVVDLKKFRKIAA  
 GDRLRGQYQGLSQDPNSLSNLDQDLPNNMIHQVPIKSLPQEWLWCETWCDDASKKRA  
 KTIDLCNNPMTKEPKLEAAVRIVPEWQDYDQEIKQLQIRFQKEKETGALYKEKTKEPSRE  
 GPQKREEL

SEQ ID No: 106

MSGGGPSGGPGGGSGRARTSSFAEPGGGGGGGGGGPGGSASGPGGTGGGKASVG  
 AMGGGVGASSSGGGPGGSGGGGGGGPGAGTSFPPPGVKLGRDSGKVTTVVATLGQ  
 GPERSQEVAUTDIKIGNGSFGVYQARLAETRELVAIKVLQDKRFKNRELQIMRKLDH

CNIVRLRYFFYSSGEKKDELYNLVLEYVPETVYRVARHFTAKLTIPILYKVYMYQLFR  
 SLAYIHSQGVCHRDIKPQNLLVDPTAVLKLCDFGSAKQLVRGEPNVSYICSRYYRAPE  
 LIFGATDYTSSIDVWSAGCVLAELLLGQPIFPGDSGVDQLVEIIKVLGTPREQIREMNP  
 YTEFKFPQIKAHWPWTKVFKSRTPPEAIALCSSLLEYTPSSRLSPLACAHSSFFDELRCLG  
 TQLPNRPLPPLFNFSAGELSIQPSLNAILIPPHLRSPAGTTLTTPSSQALTETPTSSDWQ  
 STDATPTLTNSS

SEQ ID No: 107

MNIQEQQFPLDLGASFTEADPRPPVPGEEGELVSTDPRPASYSFCSGKGVGKGETST  
 ATPRRSDLDLGYEPEGSASPTPPYLKWAESLHSLLDDQDGISLFRTFLKQEGCADLLDF  
 WFACTGFRKLEPCDSNEEKRLKLARAIYRKYILDNNNGIVSRQTKPATKSFIKGCIKMQLID  
 PAMFDQAQTEIQATMEENTYPSFLKSDIYLEYTRTGSESPKVCSDQSSGSGTGKGISGY  
 LPTLNEDEEWKCDQDMDEDGRDAAPPGRLPQKLLLETAAPRVSSSRYYSEGREFRY  
 GSWREPVNPNYYVNAGYALAPATSANDSEQQSLSSADTLSLTSSVDGIPPYRIRKQH  
 RREMQESVQVNNGRVPLPHIPRTYRVPKEVRVEPQKFAEELIHRLEAVQRTREAEEKLEE  
 RLKRVRMEEEGEDGDPSSGPPGPCHKLPPAPAHHFPPRCVDMGCAGLRDAHEENP  
 ESILDEHVQRVL RTPGRQSPGPGRSPDGHVAKMPVALGGAASGHGKHVPKSGAKL  
 DAAGLHHHRHVHHVHHSTARPKEQVEAEATRRAQSSFAWGLEPHSHGARSRGYSE  
 SVGAAPNASDGLAHSGKVGVACKRNAAKKAESGKSASTEVPGASEDAEKNQKIMQWIIE  
 GEKEISRHRRRTGHGSSGTRKPQPHENSRLSLEHPWAGPQLRTSVQPSHLFIQDPTMP  
 PHPAPNPLTQLEEARRLEEEKASRAPSQKQRYVQEVMRRGRACVRPACAPVLHVV  
 PAVSDMELSETETRSQRKVGGGSAQPCDSIVVAYYFCGEPIPYRTLVRGRAVTLGQFK  
 ELLTKKGSYRYYFKKSDEFDCGVVFEEVREDEAVLPVFEEDIIGKVEKVD

SEQ ID No: 108

MPCRREEEEEAGEEEAEGEAAAAEDSFLLLQQSVALGSSGEVDRLVAQIGETLQLDAAXD  
 SPASPCGPPGAPLRAPGPLAAAVPADKARSPAVPLLPPALAETVGPAPPGVLRCALG  
 DRGRVRGRAAPYCVAELATGPSALSPLPPQADLDGPPGAGKQGIPQPLSGPCRRGWL  
 RGAAASRRLQQRRGSQPETRTGDDDPHRLLQQQLVLSGNLIKEAVRRLHSRRRLQLRAKL  
 PQRPLLGPLSAPVHEPPSPRSPRAACSDPGASGRAQLRTGDGVLPGS

SEQ ID No: 109

MPCRREEEEEAGEEEAEGEAAAAEDDSFLLLQQSVALGSSGEVDRLVAQIGETLQLDAAQD  
 SPASPCAPPGVPLRAPGPLAAAVPADKARPPAVPLLPPASAETVGPAPSGALRCALG

DRGRVRGRAAPYCVAEVAAGPSALPGPCRRGWLRAVTSRRLQQRRWTQAGARAG  
 DDDPHRLLQQLVLSGNLIKEAVRRLQRAVAAVAATGPASAPGPGGGRSGPDRIALQPS  
 GSLL

SEQ ID No: 110

MNVQEQQFPLDLGASFTEDAPRPPVPGEEGELVSTDSPVNHSFCSGKGTSIKSETST  
 ATPRRSDLDLGYEPEGSASPTPPYLWAEHLHSLDDQDGISLFRTFLKQEGCADLLDF  
 WFACSGFRKLEPCDSNEEKRLKLARAIYRKYILDSNGIVSRQTKPATKSFIKDCVMKQQI  
 DPAMFDQAQTEIQSTMEEENTYPSFLKSDIYLEYTRTGSESPKVCSDDQSSGSGTGKGMS  
 GYLPTLNEDEEWKCDQDADEDDGRDSVPPSRLTQKLLLETAAPRAPSSRRYNEGREL  
 RYGSWREPVPNPYYVNSGYALAPATSANDSEQQSLSSADTLSLTSSVDGIPPYRIRK  
 QHRREMQESVQVNGRVPLPHIPRTYRMPKEIRVEPQKFAEELIHRLEAVQRTREAEKL  
 EERLKRVRMEEEDEDGEMPSGPMASHKLPSVPAWHFPPRYVDMGCSGLRDAHEEN  
 PESILDEHVQRVMRTPGCQSPGPGRSPDGHVAKTAVLGGTASGHGKHAPKLGLKL  
 DSAGLHHHRHVHHVHNSARPKEQMEAEEAARRVQSSFSWGPETHGHAKPRSYSES  
 TGTNPSAGDLAFGGKASAPSKRNTKKAESGKNASAEEVPSSTTEDAEKNQKIMQWIIEGE  
 KEISRHRKAGHGSSGMRKQQAHESSRPLSIERPGAVHPWVSAQLRNSVQPShLFQDP  
 TMPPNPAPNPLTQLEEARRLEEEKANKLPSKQRTKSQRKAGGGSAPPCCDSIVVAY  
 YFCGEPIPYRTLVRGRAVTLGQFKELLTKKGSYRYYFKVSDEFDCGVVFEEVREDEAI  
 LPVFEEKIIGKVEKVD

SEQ ID No: 111

MATFRNNHMKTASVRKSFSEDVFQSVKSLLQSQKELCSVTAEDCLQQDEHANLTEVT  
 FLGFNEETDAAHIQDLAAVSLELPDILNSLHFCSLNENEIICMKNINKPLDISSDPLNQSHP  
 SGMLCVMRVSPTSPRLRIDFIFSLLSKYATGIRYTLDTFLHQKHQLETTDEDDDTNQSV  
 SSIEDDFVTAFEHLEEEETSKPYNDGMNITVLRSQCDAAASQTVTGHILETHDLKILISSG  
 QQKSLAKPSTSSNVNLGHKELPSVKTSVTTSISEPWTQRSFYRSSNASDKDSLQKTF  
 SSSPAYSSESECSSPSPVIFLDEEGYQKSLKAKLELPKIPVMKDDIEDSDSEVSEFFDSF  
 DQFDELEQTLETCLFNKDPVIGKSSQRKGKHKGKSCMNPQKFDRPALPANVRKPTP  
 RKPESPYGNLCDAPDSPRPVKASREDSGLFSPRSSAFSPLGGCTPAECFCQTDIGGD  
 RIHENHDSVYYTYEDYAKSISCEVLGSQLRTHHTNTLSNINSIKGENKVTFKHGNLDQ  
 KNKSKNKSMLIKDSIQKFAADLVEKSFSAFKDLQKGVSSCTNALYHLAIKLSSVLQMA  
 FDELRRQRQAFSLKERAISGLANFLVSEALSNALKDLQYVKKQIFTNTVARFAADLAELV  
 FEGIMEVCQFSYPQTPASPQCGSFDFEDKVVKLYAKDLSESVIQEAFIELSQVDVTFTTK

AAVSVSTDNIKYVSAESVPSTQAVTFSPSFHNQAIMVTKPVQEYKKEYTVQQALFCTS  
 GIVTSIPVPLAGSALLPYHISSTACQAKAHLSSDDNSNGDSAQVHIATKNREEKAACLR  
 NICLPSEHNPQNQNDFKPTNDDIEMQSSSKLPNDPAIISNFSAAVVHTIVNETLESMTSL  
 EVTKMVDERTDYLTKSLKEKTPPFSHCDQAVLQCSEASSNKDMFADRLSKSIKHSIDKS  
 KSVIPNIDKNavyKESLPVSGEESQLTPEKSPKFDPDSQNQLTHCSLSAAKDCVPECKVS  
 MVHGSSLETPSCPAVTGQKSDLKESAKDQPLKKHNLNSTSLEALSGQENPFPHSHT  
 FSSTALTCDGLHVEDKQKVRDRNVIPDTPPSTPLVPSRASSEWDIKLTKKLKGELAK  
 EFAPATPPSTPHNSSVGSLSENEQNTIEKEE FMLKLMRSLSSEEVESSES GELPEVDVKS  
 EHSGKKVQFAEALATHILSLATEMAASHLDNKIIQEPKVKNPCLNVQSQRVSPTFLNPS  
 DENLKTLCNFAGDLAAEVITEAEKIAKVRNCMLFKQKKNSCYADGDEDYKVEEKLDIEAV  
 VHPREVDPFILSLPPSSCMGLMYKYPSCESVTDEYAGHLIQILKQEGGNSELMDQYA  
 NRLAYRSVKSGLQEAAKTTKVQCNSRMFPVPSSQVKTNKELLMFSNKEHHQEADKKR  
 QSKRNEGYFCKNQTCERTLDPYRNEVSQQLYSFSTSLVHSITKDACEELTASLVGLPKSL  
 TDSCLFEKSGYEEDNECHVTPELPKSLQPSSQNHRFYHSTGSLNGYCGDNVVQAVE  
 QYAKKVVDDTLELTGSTVFRVSETTKSADRVTYAEKLSPLTGQACRYCDLKELNCTG  
 NSSQHFFRQGSLOSSKPASNPKFSSRYQKSRIFHLSVPQIHVNLDKKAVLAEKIVAEAIE  
 KAERELSSTS LAADSGIGQEGASFAESLATETMTAAVTNVGHAVSSSKEIEDFQSTESV  
 SSQQMNL SIGDDSTGSWSNLSFEDEHQDESSSFHHLSESNGNSSWSSLGLEGDLYE  
 DNLSFPTSDSDGPDDKDEEHEDeveGLQDGKTLITNIIDMEPCTVDPQLRIILQWLIAS  
 EAEVAELYFHDSANKEFMLS KQLQEKGWKGVDLLQAVLQYYEVMEKASSEERCKSLF  
 DWLLENA

SEQ ID No: 112

METDCNPMELSSMSGFEEGSELNGFEGTDMKDMRLEAEAVVNDVLFAVNNMFVSKSL  
 RCADDVAYINVETKERNRYCLELTEAGLKVVGYAFDQVDDHLQTPYHETVYSLDTLSP  
 AYREAFGNALLQRLEALKRDGQS

SEQ ID No: 113

TSSRAVC SAAAAAAAAA ALSVWPAGPVGVCSRTDEQRVAVLRQLEMSEPKAIDPKLSTT  
 DRVVKAVPFPPSHRLTAKEVFDNDGKPRVDILKAHLMKEGRLEESVALRIITEGASILRQ  
 EKNLLDIDAPVTVCVDIHGQFFDLMKLFEVGGSPANTRYLFLGDYVDRGYFSIECVLYL  
 WALKILYPKTLFLRGNHCRHLTEYFTFKQECKIKYSERVYDACMDAFCPLAALMN  
 QQFLCVHGGLSPEINTLDIRKLDRFKEPPAYGPMCDILWSDPLEDFGNEKTQEHFTHN  
 TVRGCSYFYSYPAVCEFLQHNNLLSILRAHEAQDAGYRMYRKSQTTGFPSLITIFAPNY

LDVYNNKAAVLKYENNVMNIRQFNCSHPYWLPNFMDVFTWSLPFGEKVTEMLVNVL  
 NICSDDELGSEEDGFDGATAAARKEVIRNKIRAIGKMARVFSVLREESESVLTLKGLTPT  
 GMLPSGVLSGGKQTLQSATVEAIEADEAIKGFPQHKITSFEEAKGLDRINERMPRRD  
 AMPSDANLNSINKALTSETNGTDSNGSNSSNIQ

SEQ ID No: 114

MAAPEPARAAPPoooooooooooooGDRVVKAVPFPPTHRLLTSEEVFDLGDIPRVDVLKNHL  
 VKEGRVDEEIALRIINEGAAILRREKTMIEVEAPITVCGDIHGQFFDLMKLFEVGGSPANT  
 RYLFLGDYVDRGYFSIEHVLGTEDISINPHNNINECVLYLWVLKILYPSTLFLLRGNHECR  
 HLTEYFTFKQECKIKYSERVYEACMEAFLDSLPLAALLNQQFLCVHGGLSPEIHTLDDIRR  
 LDRFKEPPAFGPMCDLLWSDPSEDGFNEKSQEHSNTVRGCSFYNYPAVCEFLQN  
 NNLLSIIRAHEAQDAGYRMYRKSQTTGFPSSLITIFSAPNYLDVYNNKAAVLKYENNVMNI  
 RQFNCSHPYWLPNFMDVFTWSLPFGEKVTEMLVNVLSCSDDLEMTEGEDQFDGS  
 AAARKEIIRNKIRAIGKMARVFSVLREESESVLTLKGLTPTGMLPSGVLAGGRQTLQSGN  
 DVMQLAVPQMWDWGTPHSFANNSHNACREFLLFFSSCLSS

SEQ ID No: 115

MVDYSVWDHIEVSDDDEDETHPNIDTASLFRWRHQARVERMEQFQKEKEELDRGCREC  
 KRKVAECQRKLKELEVAEGGKAELRLQAEAQQLRKEERSWEQKLEEMRKKEKSMPW  
 NVDTLSKDGFSKSMVNTKPEKTEEDSEEVREQHKTFVEKYEKQIKHFGMLRRWDDS  
 QKYLSDNVHLVCEETANYLVIWCIDLEVEEKCALMEQVAHQTVMQFILELAKSLKVDPR  
 ACFRQFFTKitADRQYMEGFNDELEAFKERVRGRAKLRIEKAMKEYEEEERKKRLGP  
 GGLDPVEVYESLPEELQKCFDVQMLQDAISKMDPTDAKYHMQRCIDSGLWVPNS  
 KASEAKEGEEAGPGDPLLEAVPKTGDEKDVS

SEQ ID No: 116

MHFRNFNYSFSSLIACVANSIFSESETRAKFESLFRTYDKDITFQYFKSFKRVRINFSNP  
 FSAADARLQLHKTEFLGKEMKLYFAQLHIGSSHAPPNPDKQFLISPPASPPVGWKQV  
 EDATPVINYDLLYAISKLGPGKEKYELHAATDTPSVVVHVCESDQEKEEEEEEMERMRRP  
 KPKIIQTRRPEYTPIHLS

SEQ ID No: 117

MGNAAAAKKGSEQESVKEFLAKAKEDFLKKWESPAQNTAHLDQFERIKTLGTGSFGRV  
 MLVKHKETGNHYAMKILDQKVVKLKQIEHTLNEKRILQAVNFPFLVKLEFSFKDNSNLY

MVMEYVPGGEMFSHLRRIGRFSEPHARFYAAQIVLTFEYLHSLDLIYRDLKPENLLIDQQ  
 GYIQVTDFGFAKRVKGRTWTCGTPEYLAPEIILSKGYNKAVDWALGVLIYEMAAGYP  
 PFFADQPIQIYEKIVSGKVRFPSHFSSDLKDLLRNLLQVDLTKRGFNLKNGVNDIKNHKW  
 FATTDWIAIYQRKVEAPFIPKFKPGDTSNFDDYEEEEIRVSINEKCGKEFSEF

SEQ ID No: 118

GNAATAKKSEVESVKEFLAKAKEDFLKKWENPTQNNAGLEDFERKTLGTGSFGRV  
 MLVKHKATEQYYAMKILDQKVVKLKQIEHTLNEKRILQAVNFPFLVRLEYAFKDNSNLY  
 MVMEYVPGGEMFSHLRRIGRFSEPHARFYAAQIVLTFEYLHSLDLIYRDLKPENLLIDHQ  
 GYIQVTDFGFAKRVKGRTWTCGTPEYLAPEIILSKGYNKAVDWALGVLIYEMAAGYP  
 PFFADQPIQIYEKIVSGKVRFPSHFSSDLKDLLRNLLQVDLTKRGFNLKNGVSDIKTHKW  
 FATTDWIAIYQRKVEAPFIPKFRGSGDTSNFDDYEEEDIRVSITEKCAKEFGEF

SEQ ID No: 119

MESGSTAASEEARSRECELYVQKHNIQALLKDSIVQLCTARPERPMAFLREYFERLEK  
 EEAKQIQNLQKAGTRTDSREDEISPPPPNPVVKGRRRRGAISAEVYTEEDAASYVRKVI  
 PKDYKTMAALAKAIEKNVLFSHLDNERSDIFDAMFSVSFIAGETVIQQGDEGDNFYVID  
 QGETDVYVNNEWATSVGEGGSFGELALIYGTTPRAATVAKTNVKLWGIDRDSYRRILM  
 GSTLRKRKMYEEFLSKVSILESLDKWERLTVADALEPVQFEDGQKIVVQGEPGDEFFIIL  
 EGSAAVLQRRSENEEFVEVGRLGPSDYFGEIALLMNRPRAATVARGPLKCVKLDRPR  
 FERVLGPCSDILKRNIQQYNSFVSLSV

SEQ ID No: 120

MLTCNKAGSRMVDAANSNGPFQPVLLHIRDVPPADQEKLFIQKLRQCCVLFDFVSD  
 PLSDLKWKEVKRAALSEMVEYITHNRNVITEPIYPEVVMFAVNMFRTLPPSSNPTGAE  
 FDPEEDEPTLEAAWPHLQLVYEFFLRFLESPDFQPNIAKKYIDQKFVLQLLELFSEDPR  
 ERDFLKTTLHRIYGKFLGLRAYIRKQINNIFYRFIYETEHHNGIAELLEILGSIINGFALPLKE  
 EHKIFLLKVLLPLHKVKSLSVYHPQLAYCVVQFLEKDSTLTEPVVMALLKYWPKTHSPKE  
 VMFLNELEEILDVIEPSEFVKIMEPLFRQLAKCVSSPHFQVAERALYYWNNEYIMSLISDN  
 AAKILPIMFPSLYRNSKTHWNKTIHGLIYNALKFMEMNQKLFDDCTQQFKAEKLKEKLK  
 MKEREAWVKIENLAKANPQVLKKRIT

SEQ ID No: 121

MEDYLQGCRAALQESRPLHWVLGNEACLDSTVSALALAFYLAKTTEAEEVFVPVLNIK  
 RSELPLRGDIVFFLQKVHIPESILIFRDEIDLHALYQAGQLTLILVDHHILSKSDTALEEAVA  
 EVLDHRPIEPKHCPPCHVSVELVGSCATLVTERILQGAPEILDRTAALLHGTIILDCVNM  
 DLKIGKATPKDSKYVEKLEALFPDLPKRNDIFDSLQKAKFDVSGLTTEQMLRKDQKTIYR  
 QGVKVAISAIYMDLEAFLQRSNLLADLHAFCQAHSYDVLVAMTIFFNTHNEPVRQLAIFC  
 PHVALQTTICEVLERSHSPPKLTPASSTHPNLHAYLQGNTQVSRRKLLPLLQEALSAFY  
 DSMKIPSGQPETADVSREQVDKELDRASNSLISGLSQDEEDPPLPPTPMNSLVDECPLD  
 QGLPKLSAEAVFEKCSQISLSQSTTASLSKK

SEQ ID No: 122

MAERESGGLGGGAASPPAASPFLGLHIASPPNFRLTHDISLEEFEDEDLSEITDECGLSL  
 QCKDTLSLRPPRAGLLSAGGGGAGSRLQAEMLQMDLIDATGDTPGAEDDEEDDDEER  
 AARRPGAGPPKAESGQEPASRGQQSQGSQGPQSGDTYRPKRPTTLNLFQVPRS  
 QDTLNNSLGKKHSWQDRVSRSSPLKTGEQTTPHEHICLSDDELPPQSGPAPTTDRGT  
 STDSPCCRSTATQMAPPGPPAAPPGRGHSHRDRIHYQADVRLEATEEIYLTPVQRP  
 PDAAEPTSAFLPPTESRMSVSSDPDPAAYPSTAGRPHPSISEEEEGFDCLSSPERAEPP  
 GGGWRGSLGEPPPPPRASLSSDTALSYDSVKYTLVVDEHAQLELVSLRPCFGDYSDE  
 SDSATVYDNCASVSSPYESAIGEEYEEAPRPQPPACLSEDSTPDEPDVHFSKKFLNVF  
 MSGRSRSSSAESFGLFSCIINGEEEQTHRAIFRFVPRHEDELELEVDDPLLVELQAED  
 YWYEAYNMRTGARGVFPAYYAIEVTKPEHMAALAKNSDWVDQFRVKFLGSVQVPHY  
 KGNDVLCAAMQKIATTRRLTVHFNPSSCVLEISVRGVKIGVKADDSQEAKGNKCSHFF  
 QLKNISFCGYHPKNNKYFGFITKHPADHRFACHVFVSEDSTKALAESVGRAFQQFYKQF  
 VEYTCPTEDIYLE

SEQ ID No: 123

MSTMVYIKEDKLEKLTQDEIISGTKQVIQGLEALKNEHNSILQSLLETLKCLKKDDESNLV  
 EEKSNMIRKSLEMLELGLSEAQVMMALSNHLNAVESEKQKLRAQVRRRLCQENQWLRD  
 ELANTQQKLQKSEQSVAQLEEEKKHLEFMNQLKYDDDISPSEDKTDSTKEPLDDLFP  
 NDEDPPGQGIQQQHSSAAAAAQQGGYEIPARLRTLHNLVIQYASQGRYEVAVPLCKQA  
 LEDLEKTSGHDHPDVATMLNILALVYRDQNKYKDAANLLNDALAIKEKTLGKDHPAVAAT  
 LNNLAVLYGKRGKYKEAEPLCKRALEIREKVLGKDHPDVAKQLNNLALLCQNQGKYEEV  
 EYYYQRALLEIYQTKLGPDDPNVAKTKNNLASCYLKQGKFQAEETLYKEILTRAHEREFG  
 SVDDENKPIWMHAEEERECKGKQKDGTSGEYGGWYKACKVDSPTVTTLKNLGALY

RRQGKFEAAETLEEAAMRSRKQGLDNVHKQRVAEVLDPENMEKRRSRESLNVDVVK  
YESGPDGGEVSMSVEWNGGVSGRASFCGKRQQQQWPGRHR

SEQ ID No: 124

MADPAECSIKVMCRFRPLNEAEILRGDKFIPFKKGDETIVIGQGKPYVFDRVLPPNTTQE  
QVYNACAKQIVKDVLEGYNGTIFAYGQTSSGKHTMEGKLHDPQLMGIIPRIAHIDIFDHIY  
SMSENLEFHVKSYFEIYLDKIRDLLVSKTNLAVHEDKNRVPYVKGCTERFVSSPEEV  
DVIDEGKANRHAVTNMNEHSSRSHSIFLINIKQENVETEKLSGKLYLVLAGSEKVSK  
TGAEGAVLDEAKNINKSLSLGNVISALAEKTTHVPRDSKMTRILQDSLGGNCRTTIVI  
CCSPSVFNEAETKSTLMFGQRAKTIKNTVSVNLELTAEEWKKYEKEKEKNKTLKNVIQ  
HLEMELNRWRNGEAVPEDEQISAKDQKNLEPCDNTPIIDNIAPVVAGISTEEKEKYDEEI  
SSLYRQLDDKDDEINQQSQLAEKLKQQMLDQDELLASTRRDYEKIQEELTRLQIENEAA  
KDEVKEVLQALEELAVNYDQKSQEVEDKTRANEQLTDELAQKTTLTQRELSQLQEL  
SNHQKKRATEILNLLKDLGEIGGIIGTNDVKTADVNGBIEEEFTMARLYISKMKSEVKSL  
VNRSKQLESAQMDSNRKMNASERELAACQLLISQHEAKIKSLTDYMQNMEQKRRQLEE  
SQDSLSEELAKLRAQEKMHEVSFQDKEKEHLTRLQDAEEMKKALEQQMESREAHQK  
QLSRLRDEIEEKQKIIDEIRDLNQKLQEKEKLSSDYNKLKIEDQEREMKLEKLLLNDKR  
EQAREDLKGLEETVSRELQTLHNLRLKFVQDLTRVKKSVLDNDDGGGSAAQKQKISF  
LENNLEQLTKVHKQLVRDNADLRCELPKLEKRLRATAERVKALESALKEAKENAMRDRK  
RYQQEVDRIKEAVRAKNMARRAHSQIAKPIRPGHYPASSPTAVHAIRGGGGSSSNST  
HYQK

SEQ ID No: 125

MADLAECNIKVMCRFRPLNESEVNQGDKYIAKFQGEDTVVIASKPYAFDRVQSSTSQE  
QVYNDCAKKIVKDVLEGYNGTIFAYGQTSSGKHTMEGKLHDPEGMGIIPRIVQDIFNYI  
YSMDENLEFHVKSYFEIYLDKIRDLLVSKTNLSVHEDKNRVPYVKGCTERFVCPDEV  
MDTIDEGKSNRHAVTNMNEHSSRSHSIFLINVKQENTQTEQKLSGKLYLVLAGSEKV  
SKTGAEGAVLDEAKNINKSLSLGNVISALAEGSTYVPRDSKMTRILQDSLGGNCRTTI  
VICCSPSSYNESETKSTLLFGQRAKTIKNTVCVNVELTAEQWKKYEKEKEKNKILRNTI  
QWLENELNRWRNGETVPIDEQFDKEKANLEAFTVDKDITLTNDKPATAIGVIGNFTDAE  
RRKCEEIAKLYKQLDDKDEEINQQSQLVEKLKTQMLDQEELLASTRRDQDNMQAELN  
RLQAENDASKEEVKEVLQALEELAVNYDQKSQEVEDKTKEYELLSDELNQKSATLASID  
AELQKLKEMTNHQKKRAAEMMASLLKDLAEIGIAVGNNNDVKQPEGTGMIDEEFTVARLY  
ISKMKSEVKTMVKRCKQLESTQTESNKKMEENEKELAACQLRISQHEAKIKSLTEYLQN

VEQKKRQLEESVDALEELVQLRAQEKVHEMEKEHLNKVQTANEVKQAVEQQIQSHRE  
 THQKQISSLRDEVEAKAKLITDLQDQNQKMMLEQERLRVEHEKLKATDQEKSRLHELT  
 VMQDRREQARQDLKGLEETVAKELQTLHNLRLFVQDLATRVKKSAEIDSDDTGGSAA  
 QKQKISFLENNLEQLTKVHKQLVRDNADLRCELPKLEKRLRATAERVKALESALKEAKE  
 NASRDRKRYQQEVDRIKEAVRSKNMARRGHSQAQIAKPIRPGQHPAASPTHPSAIRGGG  
 AFVQNSQPVAVRGGGGKQV

SEQ ID No: 126

MATQADLMELDMAMEPDRKAAVSHWQQQSYLDSGIHSGATTAPSLSGKGNPEEEDV  
 DTSQVLYEWEQGFSQSFTQEQQVADIDGQYAMTRAQRVRAAMFPETLDEGMQIPSTQF  
 DAAHPTNVQRLAEPSQLKHAVVNLINYQDDAELATRAIPELTKLLNDEDQVVVNKA  
 MVHQLSKKEASRHAIMRSPQMVSIAVRTMQNTNDVETARCTAGTLHNLSHHREGLLAIF  
 KSGGIPALVKMLGSPVDSVLFYAITTLHNLLLHQEGAKMAVRLAGGLQKMVALLNKT  
 NVKFLAITTDCLQILAYGNQESKLIILASGGPQALVNIMRTTYEKLLWTTSRVLKVLSVCSS  
 NKPAIVEAGGMQALGLHLTDPSQRLVQNCLWTLRNLSDAATKQEGMEGLLGT  
 LVQLLSDDINVVTCAAGILSNLTCNNYKNKMMVCQVGGIEALVRTVLRAGDREDITEPAICALRH  
 LTSRHQEAEAMAQN  
 A V R L H Y G L P V V V K L L H P P S H W P L I K A T V G L I R N L A C P A N H A P L R E  
 QGAIPRLVQLLVRAHQDTQRRTSMGGTQQQFVEGVRMEEIVEGCTGALHILARDVHNR  
 IVIRGLNTIPLFVQLLYSPIENIQRVAAGVLCELAQDKEAAEAIEAEGATAPLTELLHSRNE  
 GVATYAAAVLFRMSEDKPQDYKKRLSVELTSSLFRTEPMANETADLGLD  
 IGAQGEPLGYRQDDPSYRSFHSGGYGQDALGMDPMMHEMGHHPGADYPVDGLPD  
 LGHAQDLMDGLPPGDSNQLAWFD  
 TDL

SEQ ID No: 127

MSSSEEVSWISWF  
 CGLRGNEFFCEVDEDYI  
 QDKFNLTGLNEQVPH  
 YRQALDMILD  
 LEPEELEDNP  
 NQSDLIEQAAE  
 MLYGLI  
 HARYILT  
 NRGIAQM  
 LEKYQQGD  
 FGYCPR  
 VYCENQ  
 PMLPIGLSD  
 IGP  
 GEAMVKLYCP  
 KCMDVYTP  
 KSSRHH  
 TDGAYFGTGF  
 PHMLFMV  
 HPEYR  
 PKRPANQF  
 VPRLYG  
 FKIHP  
 MAYQL  
 QLQA  
 ASNFK  
 SPVKT  
 IR

SEQ ID No: 128

MSWVQATLLARGLCRAWGGTCGAALTGTSISQV  
 PRRLPRGLHCSAAAHS  
 SEQSLVPS  
 PPEPRQRPTK  
 ALVPFEDLFGQAP  
 GGERDKASFL  
 QT  
 VQKFAEH  
 SVRKRG  
 HIDFIY  
 LALRK  
 MREYGVER  
 DLAVYN  
 QLLN  
 IFPK  
 EVFR  
 PRNII  
 QRIF  
 VHY  
 PRQQ  
 ECGIA  
 VLE  
 QMENHG  
 VMP  
 NKETEF  
 LIQIFGR  
 KSYP  
 MLKL  
 VRLKL  
 WFPR  
 FMNV  
 NP  
 FPV  
 PRDLP  
 QDP  
 VELAM  
 FGLRH  
 M

EPDLSARVTIYQVPLPKDSTGAADPPQPHIVGIQSPDQQAALARHNPARPVFVEGPFL  
 WLRNKCYYYHILRADLLPPEEREVEETPEEWNLYYPMQLDLEYVRSGWDNYEFDINEV  
 EEGPVFAMCMAGAHDQATMAKWIQGLQETNPTLAQIPVVFRLAGSTRELQTSSAGLEE  
 PPLPEDHQEEEDNLQRQQQGQS

SEQ ID No: 129

MFFSMGFIVAVKGKIASPLEAPVFVAAPHSTFFDGIACVVAGLPSMVSRNENAQVPLIGR  
 LLRAVQPVLVSRVDPDSRKNTINEIIKRTTSGGEWPQILVFPEGTCNRSCLITFKPGAFI  
 PGVPVQPVLRYPNKLDTVTWQGYTFIQLCMLTCQLFTKVEVEFMPVQVPNDEEK  
 NDPVLFANKVRNLMAEALGIPVTDHTYEDCRLMISAGQLTLPMEEAGLVEFTKISRKLKD  
 WDGVRKHLDEYASIASSSKGGRIGIEEFAKYLKLPVSDVRLQLFALFDRNHGSIDFREY  
 VIGLAVLCNPSNTEEIIQVAFKLFVDDEDGYITEEEFSTILQASLGVPDLDVSLFKEIAQG  
 DSISYEEFKSFALKHPEYAKIFTTYLDLQTCHVFSLPKEVQTPSTASNKVSPEKHEEST  
 SDKKDD

SEQ ID No: 130

MAATALLEAGLARVLFYPTLLYTLFRGKVPGRAHRDWYHRIDPTVLLGALPLRSLTRQLV  
 QDENVRGVITMNEEYETRFLCNSSQEWFRLGVEQLRLSTVDMTGIPTLDNLQKGVQFA  
 LKYQSLGQCVCYVHCKAGRGRSATMVAAYLIQVHKWSPEEAVERAIKIRSYIHIRPGQLDV  
 LKEFHKKQITARATKDGTAVISKT

SEQ ID No: 131

MTKFGFLRLSYEKQDTLLKLLILSMAAVLSFSTRLFAVLRFESVIHEFDPYFNYRTTRFLA  
 EEEGFYKFHNWFDDRAWYPLGRIIGGTIYPGLIMITSAAIYHVLHFFHITIDIRNCVFLAPLF  
 SSFTTIVTYHLTKEKDAGAGLLAAAMIAAVVPGYISRSVAGSYDNEGIAIFCMLLTYYMWI  
 KAVKTGSICWAACKCALAYFYMVSSWGGYVFLINLIPLHVLVLMLTGRFSHRIYVAYCTVY  
 CLGTLISMQISFVGFPQVLSSEHMAAFGVFGLCQIHAFVDYLRSKLNPPQQFEVLFRVIS  
 LVGFVLLTVGALLMLTGKISPWTGRFYSLLPSYAKNNIPIIASVSEHQPTTWSSYYFDLQ  
 LLVFMFPVGLYYCFSNLSDARIFIIMYGVTSMYFSAVMVRLMLVLAPVMCILSGIGVSQVL  
 STYMKNLDISRPDKSKKQQDSTYPIKNEVASGMILVMAFFLITYTFHSTWVTSEAYSSP  
 SIVLSARGGDGSRIIFDDFREAYYWLHNTPEDAKVMSWWDYGYQITAMANRTILVDNN  
 TWNNTHISRVGQQAMASTEEKAYEIMRELDVSYVLVIFGGLTGYSSDDINKFLWMVRIGG  
 STDTGKHICKENDYYTPTGEFRVDREGSPVLLNCLMYKMCYYRFGQVYTEAKRPPGFDR  
 VRNAEIGNKDFELDVLEEAYTTEHWLVRIYKVKDLDNRGLSRT

SEQ ID No: 132

MNLERVSNEEKLNLCKYYLGGFAFLPFLWVNIFWFFREAFLVPAYTEQSQIKGYVWR  
SAVGFLFWVIVLTSWITIFQIYRPRWGALGDYLSFTIPLGTP

SEQ ID No: 133

EAPGSSVKPVLCIHSARAGKWSLGGAEQQRLSPGPPVPSLTCLPSARMATITCTRF  
TEYQLFEELGKGAFSVRRVCVKVLAGQEYAAKIINTKKLSARDHQKLEREARICRLLKH  
PNIVRLHDSISEEGHHYLIFDLVTGGELFEDIVAREYYSEADASHCIQQILEAVLHCHQMG  
VVHRDLKPENLLASKLGAAVKLADFGLAIEVEGEQQAWFGFAGTPGYLSPEVLRKDP  
YGKPVDLWACGVILYILLVGYPFWDEDQHRLYQQIKAGAYDFPSPEWDTVTPEAKDLI  
NKMLTINPSKRITAAEALKHPWISHRSTVASCMHRQETVDCLKKFNARRKLKGAILTTML  
ATRNFSGGKSGGNKKSDGVKESSESTNTTIEDEDTKVRKQEIIKVTEQLIEAISNGDFES  
YTKMCDPGMTAFEPEALGNLVEGLDFHRFYFENLWSRNSKPVHTTILNPHIHLMGDES  
ACIAYIRITQYLDAGGIPTAQSEETRVWHRRDGKWQIVHFHRSGAPSVLPH

SEQ ID No: 134

MAAQCVTKVALNVSCANLLDKDIGSKSDPLCFLNTSGQQWYEVERTERIKNCLNPQF  
SKTFIIDYYFEVVQKLKFGVYIDNKTIELSDDDFLGECECTLGQIVSSKKLTRPLVMKTG  
RPAGKGSITISAEEIKDNRVVLFEMEARLKDNKDLFGKSDPYLEFHQQTSDGNWLMVHR  
TEVVKNLNPWRPFKISLNSLCYGDMDKTIKVECYDYDNDGSHDLIGTFQTTMTKLKE  
ASRSSPVEFECINEKKRQKKSYKNSGVISVKQCEITVECTFLDYIMGGCQLNFTGVDF  
TGSNGDPRSPDSLHYISPNGVNEYLTALWSVGLVIQDYDADKMFPAGFGAQIPPQWQ  
VSHEFPMFNPSPNPSNPYCNGIQGIVEAYRSCLPQIKLYGPTNFSPINHVARFAAAATQQQT  
ASQYFVLLIITDGVITLDDETRQAIVNASRLPMSIIIVGVGGADFSAMEFLGDGGSLRSPL  
GEVAIRDIVQFVFRQFQNAPKEALAQCVLAEIPQQVVGYFNTYKLLPPKNPATKQQKQ

SEQ ID No: 135

RRRRPSSSRRRLRGAAQMACPALGLEALQPLQPEPPPPEAFSEAQKWIEQVTGRSF  
GDKDFRTGLENGILLCELLNAIKPGLVKKINRLPTPIAGLDNIILFLRGCKELGLKESQLFD  
PSDLQDTSNRTVKSLDYSRKLKNVLVTIYWLGKAANSCTS YSGTTLNLKEFEGLLAQMQ  
RKDTDDIESPKRSIRDGYIDCWDSERSDSLSPRHRDDSFDSLDSFGSRSRQTPSP  
DVVLRGSSDGRGSDSES DLPHRKL PDVKDDMSARRTSHGEPKSAVPFNQYLPNKS  
QTAYVPAPLRKKAAEREERYRKS WSTATSPLGGERPFRYGPRTPVSDAESTSMFDMR

CEEEAAVQPHSRARQEQLQLINNQLREEDKWQDDLARWKSRRRSVSQDLIKKEEER  
 KKMEKLLAGEDGTERRSIKYREIVQEKERRELHEAYKNARSQEEAEGILQQYIE  
 RFTISEAVLERLEMPKILERSHSTEPNLSSFLNDPNPMKYLQQSLPPPFTATVETTIAR  
 ASVLDTSMSAGSGSPSKTVTPKAVPMLTPKPYSQPKNSQDVLFKVDGKVSVNGETV  
 HREEEKERECPVTAPAHSLTKSQMFEVARVHGSPLELKQDNGSIEINIKKPNSVPQEL  
 AATTEKTEPNSQEDKNDGGKSRKGNIELASSEPQHFVVTRCSPTVAFVEFPSSPQLK  
 NDVSEEKDQKKPENEMSGKVELVLSQKVVKPKSPEPEATLTFPFLDKMPEANQLHLPN  
 LNSQVDSPSSEKSPVTPQFKFWADPEEERRQEKWQQEQRLLQERYQKEQDKL  
 KEEWEKAQKEVEEEEERRYEEERKIIEDTVVPFTVSSSSADQLSTSSSMTEGSGTMNKI  
 DLGNQCQDEKQDRRWKKSFQGDDSDLLLKTRESDRLEEKGSLTEGALAHSGNPVSKGV  
 HEDHQLDTEAGAPHCGTNPQLAQDPSQNQQTSNPTHSEDVKPKTLPLDKSINHQIES  
 PSERRKKSPREHFQAGPFSPCSPTPPGQSPNRSISGKKLCSSCGLPLGKGAAIIIETLN  
 LYFHIQCFRCGICKGQLGDAVSGTDVRIRNGLLNCNDCYMRSRSAGQPTTL

SEQ ID No: 136

MAAEWASRFWLWATLLIPAAAVYEDQVGKFDWRQQYVGKVKFASLEFSPGSKKLVVA  
 TEKNVIAALNSRTGEILWRHVDKGTAEGAVDAMLLHGQDVITVNGGRIMRSWETNIGG  
 LNWEITLDSGSFQALGLVGLQESVRYIAVLKKTTLALHHLSSGHLKWEHLPESDSIHQY  
 MVYSYSGGVWALGVVFHNVNIVKFNFEDGEIVQQRVSTPWLQHLSGACGVVDEA  
 VLVCMDPSSRSLQTLALETEWELRQIPLQSLDLEFGSGFQPRVLPTQPNPVDASRAQFF  
 LHLSPEHYALLQYHYGTLSSLKNFPQTALVSFATTGEKTVAAVMACRNEVQKSSSEDG  
 SMGSFSEKSSSKDSLACFNQTYTINLYLVEGRRLDDTTFSLEQSGTRPERLYIQVFLK  
 KDDSVGYRALVQTEDHLLLFLQQLAGKVVLWSREESLAEVVCLEMVDLPLTGAQAELE  
 GEFGKKADGLLGMFLKRLSSQLILLQAWTSHLWKMFYDARKPRSQIKNEINIDTLARDEF  
 NLQKMMVMVTASGKLFGIESSSGTILWKQYLPNVKPDSSFKLMVQRTTAHFPHPPQCT  
 LLVKDKESGMSSLYVFNPIFGKWSQVAPPVLKRPILQSLLPVMDQDYAKVLLIDDEYK  
 VTAFPATRNVLRQLHELAPSIFFYLVDAEQGRLCGYRLRKDLTTELSEWLTIPPEVQRIV  
 KVKGKRSSEHVHSQGRVMGDRSVLYKSLNPNLLAVVTESTDAHHERTFIGIFLIDGVTG  
 RIIHSSVQKKAKGPVHIVHSENWWVYQYWNTKARRNEFTVLELYEGTEQYNATAFSSL  
 RPQLPQVLQQSYIFPSSISAMEATITERGITSRHLLIGLPSGAILSLPKALLDPRRPEIPTE  
 QSREENLIPYSPDVQIHAERFINYNQTVSRMRGIYTAPSGLESTCLVVAYGLDIYQTRVY  
 PSKQFDVLKDDYDYVLISSVLFGLVFATMITKRLAQVKLLNRAWR

SEQ ID No: 137

MERPWGAADGLSRWPHGLLLLLLQLLPPTLSQDRLDAPPPPAAPLPRWSGPIGVS  
 WGLRAAAAGGAFPRGGRWRRSAPGEDEECGRVRDFVAKLANNTHQHVFDDLGSVS  
 LSWVG DSTGVILVLTTFHVPLVIMTFGQSKLYRSEDYGNFKDITDLINNTFIRTEFGMAI  
 GPENSGKVVLTAEVSGGSRGGRIFRSSDFAKNFVQTDLPFHPLTQMMYSPQNDSYLLA  
 LSTENGLWVSKNFGGKWEELHKAVCLAKWGSNTIFFTYANGSCKADLGAELEWR  
 DLGKSFKTIGVKIYSFGLGGRFLFASVMADKDTRRIHVSTDQGDTWSMAQLPSVGQE  
 QFYSILAANDDMVFMHVDEPGDTGFGTIFTSDDRGIVYSKSLDRHLYTTGGETDFTNV  
 TSLRGVYITSVLS EDNSI QTMITFDQGGRWTHLRKPENSECDATAKNKNECSLHIHASY  
 SISQKLNVPMAPLSEPN AVGIVIAHGSVGDAISVMVPDVYISDDGGYSWTKMLEGPHYY  
 TILDGGIIVAI EHSRPINV KFSTDEGQCWQTYTFTRDPIYFTGLASEPGARSMNISIWG  
 FTESFLTSQWVSYTIDFKDILER NCEEKDYTIWLAHSTDPE DYEDGCILGYKEQFLRLRK  
 SSMCQNGRDYVVTKQPSICLCSLEDFLCDFGYYRPENDSKCVEQPELKGDLEFCLYG  
 REEHLTNGYRKIPGDKCQGGVNPVREVKDLKKCTSNFLSPEKQNSKSNSVPIILAIVG  
 LMLTVVAGVLIVKKYVCGGRFLVHRYSVLQQHAEANGVDGVDALDTASHTNKSGYHD  
 DSDEDLLE

SEQ ID No: 138

MLTFMASDSEEVCDERTSLMSAESPTPRSCQEGRQGPEDGENTAQWRSQENEEDG  
 EEDPDRYVCSGVPGRPPGLEEELTLKYGAKHVINLFPVTLCMIVVVATIKSVRFYTEKN  
 GQLIYTPFTEDTPSVGQRLLNSVLNTLIMISVIVVMTIFLVVLYKYRCYKFIHGWLIMSSL  
 LLFLFTYIYLGEVLKTYNVAMDYPTLLLTVWNFGAVGMVICHWGPLVLQQAYLIMISAL  
 MALVFIKYLPEWSAWVILGAI SVYDLVAVLCPKGPLRMLVETAQERNEPIFPALIYSSAM  
 WTVGMAKLDPSSQGALQLPYDPEMEEDSYDSFGEPSYPEVFEPLTGYPGEELEEEE  
 ERGVKLGLGDFIFYSVLVGKAAATGSGDWNTTLACFVAILIGLCLLLLAVFKKALPALPI  
 SITFGLIFYFSTDNLVRPFMDTLASHQLYI

SEQ ID No: 139

MGSGPLSLPLALSPPRLLLLLSSLLPVARASEAEHRLFERLFEDYNEIIRPVANVSDPVII  
 HFEVSQLVKVDEVNQIMETNLWLQIWNDYKLKWNP SDYGGAEFMRVPAQKIWK  
 DIVLYNNAVGDFQVDDKTKALLKYTGEVTWIPPAIFKSSCKIDVTYFPFDYQNCTMKFGS  
 WSYDKAKIDLVLIGSSMNLKD YWESGEWAIKAPGYKHDIKYNCCEEIYPDITYSLYIRRL  
 PLFYTI NLIIPCLLISFLTVLVFYLPSDCGEKVTLCISVLLSLTVFLLVITETIPSTS  
 LVIPLIGEY LLFTMIFVTL SIVITVFLNVHYRTPTTHTMP SWVKT VFLNLLPRVMFMRPTSNEGNAQ  
 KPRPLYGAELS NLNCFSRAESKGCKEGYPCQDGMCYCHHRRIKISNFSANL TRSSSS

ESVDAVLSLSALSPEIKEAIQSVKYIAENMKAQNEAKEEQKAQEIQQLKRKEKSTETSDQ  
EPGL

SEQ ID No: 140

MSSAPRRPAKGADSFCTPEPESLGPGLPGFPEQEEDELHRTLGVERFEEILQEAGSRG  
GEEPGRSYGEEDFEYHRQSSHIIHHPLSTHLPPDARRRKTPQGPGRKPRRRPGASPT  
GETPTIEEGEDEDEASEAEGARALTQPSPVSTPSSVQFFLREDDSADRKAERTSPSSP  
APLPHQEATPRASKGAQAGTQVEEAEAEAVAVASGTAGGDDGGASGRPLPKAQPGH  
RSYNLQERRRIGSMTGAEQALLPRVPTDEIEAQTLATADLLMKSHRFEDVPGVRRHLV  
RKNAGSTQSGREGREPGPTPRARPRAPHKPHEVFVELNELLDKNQEPMQWRETAR  
WIKEFEDVEEETERWGKPHVASLSFRSLLELRRTLAHGAVLLDLDQQTLPGVAHQVVE  
QMVISDQIKAEDRANVLRA LLKHSHPSDEKDFSPRNISAGSLGSLLGHGGQGAESD  
PHVTEPLMGGVPETRLEVERERDVPPPAPPAGITRSKS KHELKLLEKIPENAEATVVLVG  
CVEFLSRPTMAFVRLREAVELDAVLEVPPVVRFLFLLGPSANMDYHEIGRSISTLMSD  
KQFHEAAYLADEREDLLTAINAFLDCSVVLPSEVQGEELLRSVAHFQRQMLKKREEQG  
RLLPTGAGLEPKSAQDKALLQMVEAAGAAEDDPLRRTGRPFGGIIRDVRRRYPHYLSD  
FRDALDPQCLAAVIFIYFAALSPAIFTFGPLLGEKTQDLIGVSELIMSTALQGVVFCLLGAQ  
PLLVIGFSGPLLVFEAFFSFCCSNHLEYLVGRWIGFWLVFLALLMVALEGSFLVRFVS  
RFTQEIFAFLISLIFIYETFYKLVKIFQEHPLHGCSASNSEVDGGENMTWAGARPTLPGP  
NRSLAGQSGQGKPRGQPNTALLSLVLMAGTFFIAFFLRKFKNRFFPGRIRRVIGDFGV  
PIAILIMVLVDYSIEDTYTQKLSVPSGFSVTAPEKRGWVINPLGEKSPFPVWMMVASLLP  
AILVFILIFMETQITTLIISKKERMLQKGSGFHLDLLIVAMGGICALFGLPWLAATVRSVT  
HANALTVMMSKAVAPGDKPKIQEVKEQRVTGLLVALLVGLSIVIGDLLRQIPLAVLFGIFLY  
MGVTSLNGIQFYERLHLLLMPKHHPDVTYVKKVRTLRMHLFATALQLLCALLWAVMST  
AASLAFPFILITVPLRMVVLTIRTDREMKCLDANEAEPVFDEREGVDEYNEMPMPV

SEQ ID No: 141

MGKGGNQGEGAAEREVSVPTFSWEIQQKHNLRDRWLVIDRKVYNITKWSIQHPGGQ  
RVIGHYAGEDATDAFRAFHPDLEFGKFLKPLLIGELAPEEPSQDHGKNSKITEDFRALR  
KTAEDMNLFKTNHVFFLLLAHIIALESIAWFTVFYFGNGWIPTLITAFVLATSQAQAGWL  
QHDYGHLSVYRKPKWNHLVHKFVIGHLK GASANWWNHRHFQHHAKPNIFHKDPDVNM  
LHVFLGEWQPIEYGKKKLKYL PYNHQHEYFFLIGPPLI PMYFQYQIIMTMIVHKNWVDL  
AWAVSYYIRFFITYIPFYGILGALLFLNFIRFLESHWFVWVTQMNHIVMEIDQEAYRDWFS

SQLTATCNVEQSFFNDWFSGHLNFQIEHHLFPTMPRHNLHKIAPLVKSLCAKHGIEYQE  
KPLLRALLDIIRSLKKSGKLWLDAYLHK

SEQ ID No: 142

MERSGWARQTFLALLGATLRARAAGYYPRFSPFFLCTHGELEGDGEQGEVLISL  
HIAGNPTYYVPGQEYHTISTSTFDGLVTGLYTSTSVCASQSIGGSSAFGFGIMSDHQ  
FGNQFMCSVASHVSHLPTTNLSFIWIAPPAGTCVNFMATATHRGQVIFKDALAQQLC  
EQGAPTDVTVPHLAEIHSDSILRDDFDSYHQLQLNPNIWECNNCETGEQCGAIMHG  
NAVTFCEPYGPRELITTGLNTTASVLQFSIGSGCRFSYSDPsiIVLYAKNNSADWIQLE  
KIRAPSNVSTIIHILYLPEDAKGENVQFWKQENLRVGEVYEACWALDNILIINSAHRQVV  
LEDSLDPVDTGNWLFFPGATVKHSCQSDGNSIYFHGNNEGSEFNFATTRDVLSTEDIQ  
EQWSEEFESQPTGWDVLGAVIGTECGTIESGLSMVFLKDGERKLCTPSMDTTGYGNLR  
FYFVMGGICDPGNSHENDIILYAKIEGRKEHTLDTLSYSSYKVPSLVSVINPELQTPATK  
FCLRQKNHQGHNRNVAVDFFHVLVPVLPSTMHSIQFSINLGCUTHQPGNSVSLEFST  
NHGRSWSLLHTECLPEICAGPHLPHSTVYSENYSGWNRITIPLPNAALTRNTRIRWRQ  
TGPILGNMWAIDNVYIGPSCLKFCSGRGQCTRHGCKCDPGFSGPACEMASQTFPMFIS  
ESFGSSRLSSYHNFYSIRGAEVSGCOGVLASGKALVFNKEGRRQLITSFLDSSQSRFLQ  
FTLRLGSKSVLSTCRAPDQPGEGVLLHYSYDNGITWKLEHYSYLSYHEPRIISVELPGD  
AKQFGIQFRWWQPYHSSQREDVWAIDEIIMTSVLFNSISLDFTNLVEVTQSLGFYLGTV  
QPYCGHDWTLCTGDSKASSMRYVETQSMQIGASYMIQFSLVMGCGQKYTPHMDN  
QVKLEYSTNHGLTWHVQEECLPSMPSCQEFTSASIYHASEFTQWRRVIVLLPQKTWS  
SATRFRWSQSYYTAQDEWALDSIYIGQQCPNMCSGHGSCDHGICRCDQGYQGTECH  
PEAALPSTIMSDFENQNGWESDWQEVIKPEQCGVISSGSSLYFSKAGKRQLV  
SWDLDTSWDFVQFYIQIGGESASCNKPDREEGVLLQYSNNNGIQWHLLAEMYFSDF  
SKPRFVYLELPAAAKTPCTRFRWWQPVFSGEDYDQWAVDDIIILSEKQKQIIPVINPTLP  
QNFYEKPAFDYPMNQMSVWMLANEGLMVKNETFCATPSAMIFGKSDGDRFAVTRDL  
TLKPGYVLQFKLNIGCANQFSSTAPVLLQYSHAGMSWFLVKEGCYPASAGKGCEGNS  
RELSEPTMYHTGDFEEWTRITIVIPRSLOSSKTRFRWIQESSSQKNVPPFGLDGVYISEP  
CPSYCSGHGDCISGVCFCDLGYAAQGTCVSNVPNHNEMFDRFEGKLSPLWYKITGA  
QVGTGCGTLNDGKSLYFNGPGKREARTVPLDTRNIRLVQFYIQIGSKTSGITCIKPRTRN  
EGLIVQYSNDNGILWHLLRELDFMSFLEPQIISIDLQDAKTPATAFRWWQPQHGKHS  
QWALDDVLIGMNDSSQTGFQDKFDGSIDLQANWYRIQGGQVDIDCLSMDTALIFTENIG  
KPRYAETWDFHVSASTFLQFEMSMGCSKPFNSHSVQLQYSLNNNGKDWHLVTEECVP  
PTIGCLHYTESSIYTSERFQNWKRTIVYLPLSTISPRTRFRWIQANYTVGADSWAIDNVVL

ASGCPWMCSGRGICDAGRCVCDRGFGGPYCVVPLPSILKDDFNGNLHPDLWPEVY  
 GAERGNLNGETIKSGTSLIFKGEGLRMLISRDLDCNTMYVQFSLRFIAKSTPERSHSILL  
 QFSISGGITWHLMDEFYFPQTTLNLFINVPLPYTAQTNATRFRLWQPYNNGKKEIWIVD  
 DFIIDGNNVNNPVMLLDTFDFGPREDNWFFYPGGNIGLYCPYSSKGAPEEDSAMVFVS  
 NEVGEHSITTRDLNVNENTIIQFEINVGCTSTRDSSSADPVRLEFSRDFGATWHLLLPLCYH  
 SSSHVSSLSTEHHPSSTYYAGTMQGWRRREVHFGKLHLCGSVRFRWYQGFYPAGS  
 QPVTWAIDNVYIGPQCEEMCNGQQGSCINGTKCICDPGYSGPTCKISTKNPDFLKDDFEG  
 QLESDRFLLMSGGKPSRKCGILSSGNLFFNEDGLRMLMTRDLDLSHARFVQFFMRLG  
 CGKGVPDPRSQPVLLQYSLNGGLSWSLLQEFLFSNNSNVGRYIALEIPLKARSGSTRLR  
 WWQPSENGHFYSPWVIDQILIGGNISGNTVLEDDFTTLDSRKWLLHPGGTKMPVCGST  
 GDALVIEKASTRYVVSTDVAVNEDSFLQIDFAASCSVTDSCYIAIELEYSDLGLSWHPL  
 VRDCLPTNVECSRYHLQRILVSDTFNKWTRITLPLPPYTRSQA TRFRWHQPAFKDQQ  
 TWAIDNVYIGDGCIDMCSGHGRCIQGNVCDEQWGGLYCDDPETSLPTQLKDNFNRA  
 PSSQNWLTVNGGKLSTVCAGAVASGMALHFSGGCSRLLVTVDLNLTNAEFIQFYFMYGC  
 LITPNRNQGVILLESVNGGITWNLLMEIFYDQYSKPGFVNILLPPDAKEIATRFRWWQP  
 RHDGLDQNDWAIDNVLISGSADQRTVMLETFSSAPVPQHERSPADAGPGVRIAFDMFM  
 EDKTSVNEHWLFHDDCTVERFCDSPDGVMCGSHDGREVYAVTHDLTPTEGWIMQFK  
 ISVGCKVSEKIAQNQIHVQYSTDFGVSWNYLPQCLPADPKCSGSVSQPSVFFPTKGW  
 KRITYPLPESLVGNPVRFRFYQKYSDMQWAIDNFYLGPGLCDNCRGHGDCREQCICD  
 PGYSGPNCYLHTLKTFLKERFDSEEIKPDLWMSLEGGSTCTECGILAEDTALYFGGST  
 VRQAVTQDLDLRGAKFLQYWGRIGSENNMTSCHRPICRKEGVLLDYSTDGGITWTLLH  
 EMDYQKYISVRHDYILLPEDALTNTTRLWWQPFVISNGIVVSGVERAQWALDNILIGGA  
 EINPSQLVDTFDDEGT SHEENWSFYPNAVRTAGFCGNPSFHLYWPNNKKDKTHNALSS  
 RELIIQPGYMMQFKIVVGCEATSCGDLH SVMLEYTKDARSDSWQLVQTQCLPSSNSIG  
 CSPFQFHEATIYNSVNSSSWKRITIQLPDHVSSSATQFRWIQKGEETEKQSWAIDHVYIG  
 EACPKLCSGHGYCTTGAICICDESFGDDCSVFSHDLPSYIKDNFESARVTEANWETIQ  
 GGVIGSGCGQLAPYAHGDSLYFNGCQIRQAATKPLDLTRASKIMFVLQIGSMSQTDSCN  
 SDLSGPHAVDKAVLLQYSVNNGITWHVIAQHQPKDFTQAQRVSYNVLEARMKGVLLR  
 WWQPRHNGTGHDQWALDHVEVVLVSTRKQNYMMNFSRQHGLRFYNRRRRSLRRY  
 P

SEQ ID No: 143

MAEQTYSWAYSLVDSSQVSTFLISILLIVYGSFRSLNMDFENQDKEKDSNNSGSFNGE  
 QEPIIGFQPMMDSTRARFLPMGACVSLLVMFFFFDSVQVVFICTAVLATIAFAFLLLPMCQ

YLTRPCSPQNKISFGCCGRFTAELLFSLSVMLVLIWVLTGHWLLMDALAMGLCVAMI  
AFVRLPSLKVSCLLSSGLIYDVFVWFSSAYIFNSNVMVKVATQPADNPLDVLSRKLHLG  
PNVGRDVPRLSLPGKLVFPSSTGSHFSMLGIGDIVMPGLLCFVLRYDNYKKQASGDSC  
GAPGPANISGRMVKSYFHCTLIGYFVGLLTATVASRIHRAAQPALLYLVPFTLLPLTM  
AYLKGDLRMWSEPFHSKSSSSRFLEV

SEQ ID No: 144

MAEPRQEFEVMEDHAGTYGLGDRKDQGGYTMHQDQEQTDAGLKESPLQTPTEDGS  
EEPSETSDAKSTPTAEDVTAPLVDEGAPGKQAAQPHTEIPEGTTAEEAGIGDTPSLE  
DEAAGHVTQARMVSKSKDGTGSDDKKAKGADGKTIATPRGAAPPQKGQQANATRIP  
AKTPPAPKTPPSSGEPPKSGDRSGYSSPGSPGSRSTPSLPTPPTREPKKVAVVR  
TPPKSPSSAKSRLQTAPVPMPDLKNVSKIGSTENLKHQPGGGKVQIINKKLDSNVQS  
KCGSKDNIKHPGGGSVQIVYKPVDSLKVTSKCGSLGNIIHHKPGGGQVEVKSEKDFK  
DRVQSKIGSLDNITHVPGGGNNKIEHKLTRENAKAKTDHGAEIVYKSPVVSGDTSPR  
HLSNVSSTGSIDMVDPQLATLADEVASASLAKQGL

SEQ ID No: 145

MDKNELVQKAKLAEQAERYDDMAACMKSUTEQGAELSNEERNLLSVAYKNVVGARRS  
SWRVVSSIEQKTEGAEEKKQQMAREYREKIELRDICNDVLSLLEKFLIPNASQAESKVF  
YLKMKGDYYRYLAEVAAGDDKKGIVDQSQQAYQEAFEISKEMQPTHPIRLGLALNFSV  
FYYEILNSPEKACSLAKTAFDEAIAELDTLSEESYKDSTLIMQLLRDNLTWTSDTQGDEA  
EAGEGEN

SEQ ID No: 146

MSGGVYGGDEVGALVDIGSYTVRAGYAGEDCPKVDFPTAIGMVVERDDGSTMIDG  
DKGKQGGPTYYIDTNALRVPRENMEAISPLKNGMVEDWDSFQAILDHTYKMHVKSEAS  
LHPVLMSEAPWNTRAKREKLTELMEHYNIPAFFLCKTAVLTAFANGRSTGLILDGATH  
TTAIPVHDGYVLQQGIVKSPLAGDFITMQCRELFQEMNIELVPPYMIASKEAVREGSPAN  
WKRKEKLPQVTRSWHNYMCNCVIQDFQASVLQVSDSTYDEQVAAQMPTVHYEFPNG  
YNCDFGAERLKIPEGLFDPNVKGSGNTMLGVSHVVTTSVGMCDIDIRPGLYGSVIVA  
GGNTLIQSFTDRLNRELSQLTPPSMRLKLIANNTVERRFSSWIGGSILASLGTFFQQMWI  
SKQEYEEGGKQCVERKCP

SEQ ID No: 147

MAFVATQGATVVDQTTLMKKYLQFVAALTDVNTPDETKLKMMQEVS FENVTSSPQY  
STFLEHIIPRFLTFLQDGEVQFLQEKPAAQQLRKLVLEIIHRIPTNEHLRPHTKNVLSVMFRF  
LETENEENVLICLIRIIIELHKQFRPPITQEIHFLDFVKQIYKELPKVNRYFENPQVIPENT  
VPPPBMVGMITTIAVKVNPREDSETRTHSIIPRGSLSLKVL AELPIIVVLMYQLYKLNINH  
VVAEFVPLIMNTIAIQVSAQARQHKLYNKEYADFIAAQIKTLSFLAYIIRIYQELVTKYSQQ  
MVKGMLQLLSNCPAETAHLRKELLIAAKHILTTELRNQFIPCMDKLFDESILIGSGYTARE  
TLRPLAYSTLADLVHHVRQHLPLSDL SLAVQLFAKNIDDESLPSSIQTMSCKLLLNLVDCI  
RSKSEQESGNGRDVLMRMLEVFLKFHTIARYQLSAIFKKCKPQSELGA VEAALPGVPT  
APAAPGPAPSPAPVPAPP PPPPPP ATPVTPAPVPPFEKQGEKD KEDKQTFQVTDCR  
SLVKTLVCGVKTITWGITSCKAPGEAQFIPNKQLQP KETQIYIKLVKYAMQALDIYQVQIA  
GNGQTYIRVANCQTVRMKEEKEVLEHFAGVFTMMNPLTFKEIFQTTVPYMVERISKNYA  
LQIVANSFLANPTTSALFATILVEYLLDR LPEMGSNV ELSNLYLKLFKLVFGS VSLFAAE  
EQMLKPHLHKIVNSSMELAQTAKEPY NYFLLRALFRSIGGGSHDLYQEFLPLL PNLQ  
GLNMLQSGLHKQHMKDLFVELCLTVPRVRLSSLPYLPMLMDPLV SALNGSQ TLV S QGL  
RTLELCVDNLQPDFLYDHIQPVRAELMQALWRTL RNPADSISHVAYRVLGKFGGSNRK  
MLKESQKLHYVVTEVQGPSITVEFSDCKASLQLPMEKAIETALDCLKSANTEPYYRRQA  
WEVIKCFLVAMMSLEDNKHALYQLLAHPNFTEKTIPNVIISHRYKAQDT PARKT FEQALT  
GAFMSAVIKDLRPSALPFVASLIRHYTMVAVAQQCGPFLPCYQVGSQP STAMFHSEEN  
GSKGMDPLVLIDAIAICMAYEEKELCKIGEVALAVIFDVASIILGSKERACQLPLFSYIVERL  
CACCYEQAWYAKLGGVVS IKFLMERLPLTWVLQNQQTFLKALLFVMMMDLTGEV SNGAV  
AMA KTTLEQLLMRCATPLKDEERAEEIVAAQEKSFHHVTHDLVREVTSPNSTVRKQAM  
HSQLVLAQVTGKS VTVIMEPHKEVLQDMVPPKKHLLRHQPANAQIGLMEGNTFC TTLQ  
PRLFTMDLN VVEHKVFY TELLNLCEAEDSALT KLPCYKSLPSLVPLRIAALNALA ACNYLP  
QSREKIIAALFKALNSTNSELQEAGEACMRKFLEGATIEVDQIHTHMRPLL MMLGDYRSL  
TLNVNRLTSVTRLFPNSFNDKFC DQM MMQH LRK WMEVVVITHKG GQRSDGNEMKICS  
AIINLFHLIPAAPQTLVKPLLEV VMKTERAMLIEAGSPFREPLIKFLTRHPSQTVELFMMEA  
TLNDPQWSRMFMSFLKH KHDARPLRDV LAANPNRFITLLPQGAQTA VRPGSPSTSTMR  
LDLQFQAIKIIISIIVKNDDSWLASQHSLVSQLRRVW VSEN FQERHRKENMAATNWKEPK  
LLAYCLLNYC KRNYGDIELLFQLLRAFTGRFLCNMTFLKEYMEEEIPKNYSIAQKRALFFR  
FVDFNDPNFGDELKAKVLQHILNPAFLYSFEKGE GEQLLGPPNPEGDN PESITSV FITKV  
LDPEKQADM LDSLRIYLLQYATLLVEHAPHHIHDNNKNRNSKLRR LMTFAWPCLLSKAC  
VDPACKYSGHLLAHIIAKFAIHKKIVLQVFHSLLKAHAMEARAI VRQAMAILTPAVPARM  
EDGHQMLTHWTRKIIVEEGHTV PQLVHILHLIVQHFKVYYPVRHHLVQHMVSAMQRLGF  
TPSVTIEQRRLAVDLSEVVIKWE LQRIKDQ QPDSDMDPNSSGEGVNSVSSSIKRGLSVD

SAQEVKRFRTATGAISAVFGRSQSLPGADSLLAKPIDKQHTDTVVNFLRVACQVNDNT  
NTAGSPGEVLSRRCVNLLKTALRPDMWPKSELKLQWFDKLLMTVEQPNQVNYGNICT  
GLEVLFSFLTVLQSPAISLSSFKPLQRGIAACMTCGNTKVLRAVHSLLSRLMSIFPTEPSTS  
SVASKYEELECLYAAVGKVIYEGLTNYEKATNANPSQLFGTLMILKSACSNNPSYIDRLIS  
VFMRSLQKMVREHLPQAASGSTEATSGTSELVMLSLELVKTRLAVMSMEMRKNFIQAI  
LTSLIEKSPDAKILRAVVKIVEEWVKNNSPMAANQTPTLREKSILLVKMMTYIEKRFPEDL  
ELNAQFLDLVNYVYRDETSGSELTAKLEPAFLSGRLCAQPLIRAKFFEVFDNSMKRRV  
YERLLYVTCSQNWEAMGNHFWIKQCIELLLAVCEKSTPIGTSCQGAMLPSITNVINLADS  
HDRAAFAMVTHVKQEPRERENSESKEEDVEIDIELAPGDQTSTPKTKELSEKDIGNQLH  
MLTNRHDKFLDTLREVKTGALLSAFVQLCHISTTLAETWVQLFPRWKILSDRQQHAL  
AGEISPFLCSGSQHQVQRDCQPSALNCFVEAMSQCVPPIRPCVLKYLGKTHNLWFRST  
LMLEHQAFEKGQLSLQIKPKQTTEFYEQESITPPQQEILDLSAELYSSLQEEDMWAGLWQ  
KRCKYSETATAIAYEQHGFFEQAQESYEKAMDKAKEHERSNASPAIFPEYQLWEDHW  
IRCSKELNQWEALTEYGQSKGHINPYLVLECAWRVSNWTAMKEALVQEVSCPKEMA  
WKVNMYRGYLAICHPEEQQLSFIERLVEMASSLAIREWRRLPVVSHVHTPLLQAAQQII  
ELQEAAQINAQGLQPTNLGRNNSLHDMKTVVKTWRNRLPIVSDDLSHWSSIFMWRQHHY  
QAIVTAYENSSQHDPSNNAMLGVHASASAIIQYGKIARKQGLVNVALDILSRHTIPTVPI  
VDCFQKIRQQVKCYLQLAGVMGKNECMQGLEVIESTNLKYFTKEMTAEFYALKGMFLA  
QINKSEEANKAFSAAVQMHDVLVKAWAMWDYLENIFVKERQLHLGVSAITCYLHACR  
HQNESKSRKYLAKVLWLLSFDDDKNLADAVDKYCIGVPPIQWLAWIPQLLTCVGSEG  
KLLLNLIISQVGRVYPQAVYFPIRTLYLTLKIEQRERYKSDPGPIRATAPMWRCRIMHMQ  
RELHPTLLSSLEGIVDQMVWFRENWHEEVLRQLQQGLAKCYSVAFEKSGAVSDAKITP  
HTLNFVKKLVSTFGVGLENVSNVSTMSSAASESLARRAQATAQDPVFQKLKGQFTTD  
FDFSVPGSMKLHNLIISKLKKWIKILEAKTKQLPKFFLIEEKCRFLSNFSAQTAEVEIPGEFL  
MPKPTHYYIKIARFMPRVEIVQKHNTAARRLYIRGHNGKIYPYLVMDNACLTESRREERV  
LQLLRLLNPCLERKRKETTKRHLFTVPRVVAVSPQMRLVEDNPSSLSLVEIYKQRCAKK  
GIEHDNPISRYYDRLATVQARGTQASHQVLRDILKEVQSNMVRPMLKEWALHTFPNAT  
DYWTFRKMFTIQLALIGFAEFVLHLNRLNPEMLQIAQDTGKLNVAYFRFDINDATGDLDA  
NRPVPFRLTPNISEFLTTIGVSGPLTASMIAVARCFAQPNFKVDGILKTVLRDEIIAWHKKT  
QEDTSSPLSAAGQOPENMDSQQQLVSLVQKAVTAIMTRLHNLAQFEGGESKVNTLVAAAN  
SLDNLCRMDPAWHPWL

MATGADVRDILELGGPEGDAASGTISKDIINPDKKSKKSSETLTFKRPEGMHREVYAL  
LYSDKKQVLEDAPPLPSDTGQGYRTVKAKLGSKKVRPWKWMPTNPARKDGAMFFH  
WRRAAEEGKDYPFARFNKTVQVPVYSEQEYQLYLHDDAWTKAETDHLFDLSRRFDLR  
FVVIHDRYDHQQFKKRSVEDLKERYYHICAKLANVRAVPGTDLKIPVFDAGHERRKEQ  
LERLYNRTPEQVAEEEYLLQELRKIEARKKEREKRSQDLQKLITAADTTAEQRRTERKAP  
KKKLPQKKEAEKPAVPETAGIKFPDFKSAGVTLSQRMKLPSSVGQKKIKALEQMLLEL  
GVELSPTPTTEELVHMFNELSDLVLLYELKQACANCEYELOMLRHRHEALARAGVLGG  
PATPASGPGPASAEPAVTEPGLGPDPKDTIIDVVGAPLTPNSRKRESASSSSVKKAK  
KP

SEQ ID No: 149

MHHGTGPQNVHQQLQRSRACPGSEGEEQPAHPNPPPSAAPFAPSASPSAPQSPSY  
QIQQLMNRSATGQNVNITLQSVGPVGGNQQITLAPLPLPSPTSPGFQFSAQPRRFEH  
GSPSYIQVTPLSQVQTQSPTQSPSPGPGQALQNVRAAGAPGPGLGLCSSPTGGFVD  
ASVLRQISLSPSSGGHFVFDGSGLTQIAQGAQVQLQHPGTPITVRERRPSQPHQS  
GGTIHHLGPQSPAAAGGAGLQPLASPHTTANLPPQISSIIQGQLVQQQVLQGPLPR  
PLGFERTPGVLLPGAGGAAGFGMTSPPPPTSPSRTAVPPGLSSLPLTSVGNTGMKKVP  
KKLEEIPPASPEMAQMRKQCCLDYHYQEMQALKEVFKEYLIELFLQHFQGNMMDFLAF  
KKKHYAPLQAYLRQNLDIEEEEEEEEEEKSEVINDEQQALAGSLVAGAGSTVETDL  
FKRQQAMPSTGMAEQSKRPRLEVGHQGVVFQHPGADAGVPLQQLMPTAQGGMPPTP  
QAAQLAGQRQSQQYDPSTGPPVQNAASLHTPLPQLPGRLLPAGVPTAALSSALQFA  
QQPVVEAQTLQIPVKTQQPNVPIPAPPSSQLPIPPSQPAQLALHVPTPGKVQVQASQ  
LSSLPQMVASTRLPVDPAPPCCRPLPTSSTSSLAPVSGSGPGSPARSSPVNRPSSAT  
NKALSPVTSRTPGVVASAPTKPQSPAQNATSSQDSSQDTLTEQITLENQVHQRIELRK  
AGLWSQRRLPKLQEAPRPKSHWDYLLEEMQWMATDFAQERRWKVAAAKLVRTVVR  
HHEEKQLREERGKKEQSRLRIAASSTAREIECFWSNIEQVVEIKLRVELEEKRKALNL  
QKVSRRGKELRPKGFDALQESSLDGMSGRKRKASISLTDDDEVDEEETIEEEANE  
VVDHQTELSNLAKEAELPLLDLMKLYEGAFLPSSQWPRPKPDGEDTSGEEDADDCPGD  
RESRKDLVLIDSLFIMDQFKAAERMNIGKPNAKDIADVTAVAЕAIPKG SARVTTSVKFNA  
PSLLYGALRDYQKIGLDWLAKLYRKNLNGILADEAGLGKTVQIIAFFAHLACNEGNWGPH  
LVVVRSCNILKWELELKRWCPLKILSYIGSHRELKAKRQEWAEPNSFHVCITSYTQFFR  
GLTAFTWRWKCLVIDEMQRVKGMTERHWEAVFTLQSQQRLLLIDSPLHNTFELWTM  
VHFLVPGISRPYLSPLRAPSEESQDYYHKVIRLHRVTQPFILRRTKRDVEKQLTKYE  
HVLKCRLSNRQKALYEDVILQPGTQEALKSGHFVNVLISILVRLQRICNHPGLVEPRHPG

SSYVAGPLEYPSASLILKALERDFWKEADLSMFDLIGLENKITRHEAELLSKKIPRKLME  
EISTSAAPAARPAAAKLKASRLFQPVQYGQKPEGRTVAFPSTHPPRTAAPTTASAAPQG  
PLRGRPPIATFSANPEAKAAAAPFQTSQASASAPRHQPASASSTAASPAHPAKLRAQTT  
AQAFTPGQPPPQPQAPSHAAGQSALPQRLVLPSSQAQARLPSGEVVKIAQLASITGPQS  
RVAQPETPVTLQFQGSKFTLSHSQFRQFTAGQPLQLQGSVLQIVSAPGQPYLRAPGPV  
VMQTVSQAGAVHGALGSKPPAGGPSPAPLTPQVGVPGRVAVNALAVGEPGTASKPAS  
PIGGPTQEEKTRLLKERLDQIYLVNERRCSQAPVYGRDLLRICALPSHGRVQWRGSDLG  
RRGKEAGPAHSYTSSSESPSELMLTCRCGESLQDVIDRVAFVIPPVVAAPPSLRVPRP  
PPLYSHRMRILRQGLREHAAPYFQQLRQTTAPRLLQFPELRLVQFDSGKLEALAILLQKL  
KSEGRRVLILSQMILMLDILEMFLNFHYLTYVRIDENASSEQRQELMRSFNRRIFCAIL  
STHSRTTGINLVEADTVFYDNDLNPMVMDAKAQEWCDRIGRCKDIHYRLVSGNSIEEKL  
LKNGTKDLIREVAAQGNDYSMAFLTQRTIQELFEVYSPMDDAGFPVKAEEFVVLSQEPS  
VTETIAPKIARPFIEALKSIEYLEEDAQKSAQEGVLGPHTDALSSDSENMPCDEEPSQE  
ELADFMEQLTPIEKYALNYLELFHTSIEQEKERNSEDAVMTAVRAWEFWNLKTLQEREA  
RLRLEQEEAELLTYTREDAYSMEYYEDVDGQTEVMPWLTPPTPPQDDSDIYLDSCMC  
LMYEATPIPEAKLPPVYVRKERKRHKTDPSAAGRKKQQRHGEAVVPPRSLFDRATPGLL  
KIRREGKEQKKNILLKQQVPFAKPLPTFAKPTAEPGQDNPEWLISEDWALLQAVKQLLEL  
PLNLTIVSPAHTPNWDLVSDVVNSCSRIYRSSKQCRNRYENVIIPREEGKSKNRPLRTS  
QIYAQDENATHTQLYTSHFDMKMTAGKRSPIKPLLGMNPQKNPKHASVLAESGINY  
DKPLPPIQVASLRAERIAKEKKALADQQKAQQPAVAQPPPPQPQPPPPPQQPPPLPQ  
PQAAGSQPPAGPPAVQPQPQPQTQPQPVQAPAKAQPAITTGGSAAVLAGTIKTSVT  
GTSMPGTAVSGNVIVNTIAGVPAATFQSINKRLASPVAPGALTTPGGSAPAQVVHTQPP  
PRAVGSPATATPDLVSMATTQGVRAVTSVTASAVVTTNLTPVQTPARSLVPQVSQATG  
VQLPGKTITPAHFQLLRQQQQQQQQQQQQQQQQQQQQQQQQQQQQQQTTTSQV  
QVPQIQQQAQSPAQIKAVGKLTPEHLIKMQKQKLQMPPQPPPPQAQSAPPQPAQVQV  
QTSQPPQQQSPQLTTVTAPRPGALLTGTIVANLQVARLTVPTSSQLSQGQMQTQAP  
QPAQVPLPKPPVSVPAAVVSSPGVTTLPMNVAGISVAIGQPQKAAGQTVVAQPVHMQ  
QLLKLKQQAVQQQKAIQPQAAQGPATVQQKITAQQITTPGAQQKVAYAAQPALKTQFLT  
TPISQAQKLAGAQVQTQIQUAKLPQVQQQTPVASIQQVASASQQASPQTVALTQAT  
AAGQQVQMIAPVTATAQVQQKLIQQQVVTASAPLQTPGAPNPAQVPASSDSPSQQP  
KLQMRVPAVRLKTPKPPCQ

MSLAGGRAPRKTAGNRLSGLLEAEEEDEFYQTTYGGFTEESGDDEYQGDQSDTEDEV  
 DSDFDIDEGDEPSSDGEAEEPRRKRRVVTAKYKEPLKSLRPRKVNTPAGSSQKAREEK  
 ALLPLELQDDGSRSRKSMRQSTAETHTRQTFLRVQERQGQSRRKGPHCERPLTQEEL  
 LREAKITEELNRSLETYERLEADKKQVHKKRKCPGIITYHSVTVPVLGEPPGKEENV  
 DIEGLDPAPSVSALTPHAGTGPVNPPARCSRTFITFSDDATFEIEWFPQGRPPKPVREV  
 CPVTHRPALEYRDPTDIPYATARAFKIREAYKKYITAHGLPPTASALGPGPPPPEPLPGS  
 GPRALRQKIVIK

SEQ ID No: 151

MAHRKLESVGSGMLDHVRVRPGPVPHSQEPESEDMEPLEGYVPEGLELAALRPESPA  
 PEEQECHNHSPGDSSSDYVNNTSEEEDYDEGLPEEEEGITYYIRYCPEDDSYLEGMD  
 CNGEEYLAHSAHPVDTDECQEAVEEWTDASAGPHPHGHEAEGSQDYPDGQLPIPEDEP  
 SVLEAHDQEEDGHYCASCASKEGYQDYYPEEANGNTGASPYRLRRGDGDLEDQEEDIDQI  
 VAEIKMSLSMTSITSASEASPEHGPEPGPEDSVEACPPIKASCSPSRHEARPKSLNLLPE  
 AKHPGDPQRGFKPKTRTPEERLKWPHEQVCNGLEQPRKQQRSDLNGPVDNNNIPETK  
 KVASFPSFVAVPGPCEPEDLIDGIIFAANYLGSTQLLSERNPSKNIRMMQAQEAVSRVKR  
 MQKAAKIKKKANSEGDAQTLTEVDLFISTQRIKVLNADTQETMMDHALRTISYIADIGNIV  
 VLMARRRMPRSASQDCIETTPGAQEGKKQYKMICHVFESEDAQLIAQSIGQAFSVAYQ  
 EFLRANGINPEDLSQKEYSDIINTQEMYNDDLIHFSNSENCNELQLEKHKGELGVVVVE  
 SGWGSILPTVILANMMNGGPAARSGKLSIGDQIMSINGTSVGLPLATCQGIKGLKNQT  
 QVKLNIVSCPPVTTVLIKRPDLKYQLGFSVQNGIICSLMRGGIAERGGVRVGHRIIEINGQ  
 SVVATAHEKIVQALSNSVGEIHMKMPAAMFRLLTGQETPLYI

SEQ ID No: 152

MTSAAPAKKPYRKAPPEHRELRLIEPGSRLEQEEPLTDAERMKLLQEENEELRRRLASA  
 TRRTEALERELEIGQDCLELELGQSREELDKFKDKFRRLQNSYTASQRTNQELEDKLHT  
 LIKKAEMDRKTLDWEIVELTNKLLDAKNTINKLEELNERYRLDCNPNAVQLKCNKSHFRN  
 HKFADLPCELQDMVRKHLHSGQEAASPGPAPSLAPGAVVPTSVIARVLEKPESSLNSA  
 QSGSAGRPLAEDVFVHDMSEGVPGDPASPPAPGSPTPQPNGECHSLGTARGSPEEEE  
 LPLPAFEKLNPyPTPSPPHPLYPGRRVIEFSEDKVIRPRNSPLPNCTYATRQAISLSLVEE  
 GSERARPSPVPSTPASAQASPHHQSPAPLTLsapassasseedllvswqrafvdrtP  
 PPAAVAQRATFGRDALPELQRHFAHSPADRDEVVQAPSARPEESELLLPTEPDSGFPR  
 EEEELNLPISPECERQSLLPINRGTEEGPGTSHTEGRRAWPLPSSSRPQRSPKRMGVHH  
 LHRKDSDLTQAQEQQGNLLN



CLAIMS

26. März 2004

1. A protein complex selected from complex (I) and comprising

(a) at least one first protein, which first protein is selected from the group of proteins in table 1, fourth column of a given complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions; and

(b) at least one second protein, which second protein is selected from the group of proteins in table 1, fifth column of said complex, or a functionally active derivative thereof, or a functionally active fragment thereof, or a homologue thereof, or a variant of said second protein encoded by a nucleic acid that hybridizes to the nucleic acid encoding said protein under low stringency conditions;

and a complex (II) comprising at least two of said second proteins,

wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

2. A protein complex comprising a first protein selected from the proteins listed in table 1, second column of a given complex or a homologue or variant thereof, or a functionally active fragment or functionally active derivative of said first protein, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said first protein under low stringency conditions, and at least one second protein selected from the group of proteins in table 1, fifth column of a given complex, or a variant or homologue thereof, or a functionally active fragment or a functionally active derivative of said second protein, the variant of said second protein being encoded by a nucleic acid that hybridizes to the nucleic acid of said second protein under low-stringency conditions, and wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C,

washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4) 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

3. A protein complex comprising the proteins selected from the proteins in table 1, third column or a homologue thereof, or a variant thereof or functionally active fragments or functionally active derivatives of said proteins, said variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low stringency conditions; wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

4. A protein complex that comprises all proteins as listed in table 1, third column for a given complex or a homologue or a variant thereof, or a functionally active fragment or a functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins under low stringency conditions, but 1 to the number of proteins listed in table 1, fifth column of said complex, or a homologue or a variant thereof, or a functionally active fragment or functionally active derivative thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of any of said proteins of said fifth column under low stringency conditions, wherein said low stringency conditions comprise hybridization in a buffer comprising 35% formamide, 5X SSC, 50 mM Tris-HCl (pH 7.5), 5 mM EDTA, 0.02% PVP, 0.02% Ficoll, 0.2% BSA, 100 ug/ml denatured salmon sperm DNA, and 10% (wt/vol) dextran sulfate for 18-20 hours at 40°C, washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1-5 hours at 55°C, and washing in a buffer consisting of 2X SSC, 25 mM Tris-HCl (pH 7.4), 5 mM EDTA, and 0.1% SDS for 1.5 hours at 60°C.

5. The complex of any of Claim 1 - 4 comprising at least one functionally active derivative of said first protein and/or a functionally active derivative of said second protein, wherein the functionally active derivative is a fusion protein comprising said first protein or said

second protein fused to an amino acid sequence different from the first protein or second protein.

6. The complex of Claim 5 wherein the functionally active derivative is a fusion protein comprising said first protein or said second protein fused to an affinity tag or label.
7. The complex of any of Claim 1 - 4 comprising a fragment of said first protein and/or a fragment of said second protein, which fragment binds to another protein component of said complex.
8. The complex of any of Claim 1 - 7 that is involved in the biochemical activity as stated in table 3.
9. A process for preparing a complex of any of Claim 1 - 8 and optionally the components thereof comprising the following steps:  
Expressing a protein of the complex, preferably a tagged protein, in a target cell, isolating the protein complex which is attached to the protein, preferably a tagged protein, and optionally disassociating the protein complex and isolating the individual complex members.
10. The process according to Claim 9 wherein the tagged protein comprises two different tags which allow two separate affinity purification steps.
11. The process according to any of Claim 9 - 10 wherein the two tags are separated by a cleavage site for a protease.
12. Component of a protein complex obtainable by a process according to any of Claim 9 - 11.
13. Construct, preferably a vector construct, comprising at least two separate nucleic acid sequences each encoding a different protein, or a functionally active fragment or a functionally active derivative thereof, or a homologue or a variant thereof, at least one of said proteins being selected from the first group of proteins according to Claim 1 (a) and

at least one of said proteins, being selected from the second group of proteins according to Claim1 (b).

14. Host cell, containing a vector comprising a construct of Claim 13 or containing several vectors each comprising at least the nucleic acid encoding at least one protein selected from the first group of proteins according to Claim1 (a) and the nucleic acid encoding at least one protein selected from the second group of proteins according to Claim1 (b).
15. An antibody or a fragment of said antibody containing the binding domain thereof, which binds the complex of any of Claim1 - 8 and which does not bind any of the proteins of said complex when uncomplexed.
16. A kit comprising in one or more containers the complex of any of Claim 1 - 8, optionally together with an antibody according to Claim 17 and/or further components such as reagents and working instructions.
17. The kit according to Claim 16 for processing a substrate of a complex of any one of Claim 1 - 8.
18. The kit according to Claim 18 for the diagnosis or prognosis of a disease or a disease risk, preferentially for a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
19. Array in which at least a complex according to any of Claim 1 - 8 and/or at least one antibody according to Claim 17 is attached to a solid carrier.
20. A process for processing a substrate of a complex of any one of Claim 1 - 8 comprising the step of bringing into contact a complex to any of Claim 1 - 8 with said substrate, such that said substrate is processed.
21. A pharmaceutical composition comprising the protein complex of any of Claim 1 - 8.

22. A pharmaceutical composition according to Claim 21 for the treatment of diseases and disorders, preferentially for diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
23. A method for screening for a molecule that binds to the complex of any one of Claim 1 - 8, comprising the following steps:
- (a) exposing said complex or protein, or a cell or organism containing said complex or said protein, to one or more candidate molecules; and
  - (b) determining whether said candidate molecule is bound to the complex or protein.
24. A method for screening for a molecule that modulates directly or indirectly the function, activity, composition or formation of the complex of any one of Claim 1 - 8 comprising the steps of:
- (a) exposing said complex, or a cell or organism containing said complex to one or more candidate molecules; and
  - (b) determining the amount of, activity of, protein components of, and/or intracellular localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent upon the function of the complex and/or product of a gene dependent on the complex in the presence of the one or more candidate molecules, wherein a change in said amount, activity, protein components or intracellular localization relative to said amount, activity, protein components and/or intracellular localization and/or a change in the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in the absence of said candidate molecules indicates that the molecule modulates function, activity, or composition of said complex.
25. The method of Claim 24, wherein the amount of said complex is determined.
26. The method of Claim 25, wherein the activity of said complex is determined.
27. The method of Claim 25, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of

said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.

28. The method of Claim 24, wherein the amount of the individual protein components of said complex are determined.

29. The method of Claim 25, wherein said determining step comprises determining whether any of the proteins listed in table 1, third column of said complex, or a functionally active fragment or a functionally active derivative thereof, or a variant or a homologue thereof, the variant being encoded by a nucleic acid that hybridizes to the nucleic acid of said protein under low-stringency conditions, is present in the complex.

30. The method of any of Claim 24 - 29, wherein said method is a method of screening for a drug for treatment or prevention of a disease or disorder, preferentially of a disease or disorder selected from the diseases or disorders such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

31. Use of a molecule that modulates the amount of, activity of, or the protein components of the complex of any one of Claim 1 - 8 for the manufacture of a medicament for the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.

32. A method for the production of a pharmaceutical composition comprising carrying out the method of Claim 24 - 29 to identify a molecule that modulates the function, activity, composition or formation of said complex, and further comprising mixing the identified molecule with a pharmaceutically acceptable carrier.

33. A method for diagnosing or screening for the presence of a disease or disorder or a predisposition for developing a disease or disorder in a subject, which disease or disorder is characterized by an aberrant amount of, component disposition of, or intracellular localization of the complex of any one of the Claim 1 - 8, comprising determining the amount of, activity of, protein components of, and/or intracellular

localization of, said complex and/or the transcription level of a gene dependent on the complex and/or the abundance and/or activity of a protein or protein complex dependent on the function of the complex and/or product of a gene dependent on the complex in a comparative sample derived from a subject, wherein a difference in said amount, activity, or protein components of, said complex in an analogous sample from a subject not having the disease or disorder or predisposition indicated the presence in the subject of the disease or disorder or predisposition in the subject.

34. The method of Claim 33, wherein the amount of said complex is determined.
35. The method of Claim 33, wherein the activity of said complex is determined.
36. The method of Claim 35, wherein said determining step comprises isolating from the cell or organism said complex to produce said isolated complex and contacting said isolated complex in the presence or absence of a candidate molecule with a substrate of said complex and determining whether said substrate is processed in the absence of the candidate molecule and whether the processing of said substrate is modified in the presence of said candidate molecule.
37. The method of Claim 33, wherein the amount of the individual protein components of said complex are determined.
38. The complex of any one of Claim 1 - 8 or the antibody or fragment of Claim 17, for use in a method of diagnosing a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.
39. A method for treating or preventing a disease or disorder characterized by an aberrant amount of, activity of, component composition of or intracellular localization of, the complex of any one of Claim 1 - 8, comprising administering to a subject in need of such treatment or prevention a therapeutically effective amount of one or more molecules that modulate the amount of, activity or, or protein components of, said complex.

40. The method according to Claim 39, wherein said disease or disorder involves decreased levels of the amount or activity of said complex.
41. The method according to Claim 39, wherein said disease or disorder involves increased levels of the amount or activity of said complex.
42. Complex of Claim 1 - 8 and/or any of the proteins listed in table 1, fifth column of said complex as a target for an active agent of a pharmaceutical, preferably a drug target in the treatment or prevention of a disease or disorder, preferentially of a disease or disorder such as neurodegenerative disease such as Alzheimer's disease and related neurodegenerative disorders.